THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME III MARCH, 1927 NUMBER 2

METASTATIC OR EMBOLIC ENDOMETRIOSIS, DUE TO THE MENSTRUAL DISSEMINATION OF ENDOMETRIAL TISSUE INTO THE VENOUS CIRCULATION*

JOHN A. SAMPSON, M.D.

(From the Gynecological and Pathological Departments of the Albany Hospital and the Albany Medical College, Albany, New York)

Over twelve years ago the writer began a series of experiments to determine the shape of the uterine cavity in normal and pathologic conditions. The technic was as follows. The uterus removed at operation or necropsy was placed in a basin of warm water and then filled with melted gelatin (about 15 per cent) containing in suspension bismuth subcarbonate or barium sulphate. This was introduced through the cervical canal by means of a syringe. After filling the uterine cavity the syringe was withdrawn, the cervix clamped in order to prevent the escape of the injection mass and the specimen placed in cold water until the gelatin had solidified. Stereoscopic roentgenograms of the uterus enabled one to obtain a clear picture of the form of the uterine cavity under various conditions and also of the lumina of the tubes if the latter were patent. In February, 1916, I removed a myomatous uterus from a patient who was menstruating at the time of the operation. On filling the uterine cavity with the injection mass I was surprised to find that it escaped from the severed uterine and ovarian veins. This was the first time that I had noticed this phenomenon. The following experiments were made. Uteri were curetted after their removal and the uterine cavity was filled with the mass. In many instances the injection mass escaped into the venous sinuses of the uterine wall and through the uterine and ovarian veins. These observations together with a

* Received for publication December 19, 1926.

description of the venous circulation of the uterus, based on the study of uteri in which the veins had been injected, were published in the year 1918 in an article [1] dealing with the escape of foreign material into the venous circulation of the uterus. It then seemed to me that bits of the uterine mucosa, occasionally, might escape into the venous circulation during menstruation. I have frequently asked pathologists if they have ever found endometrial tissue in the lungs of women but have not ascertained that it has ever been observed.

As a result of these studies it is natural that I should consider the menstrual changes in the uterine mucosa a means of the dissemination of bits of endometrial tissue into the uterine circulation and as a possible source of certain instances of misplaced endometrial tissue in that organ and outside of it. To me it was a most plausible theory but lacked proof. I believed, however, that it must occur and could be demonstrated. It was just a question of a better knowledge of the venous and lymphatic circulations of the uterus and the histologic study of many sections of uteri, especially of those removed during menstruation.

The Intrinsic Blood Supply of the Uterus

The blood supply of the uterus was studied by injecting the vessels with melted gelatin containing bismuth subcarbonate and hardening the specimen in formalin. Stereoscopic roentgenograms were made of the entire uterus and also of cross slices of the same. The fine branches were studied in microscopic sections.

The general plan of the distribution of the intrinsic arteries of the uterus is as follows. Branches arise in pairs from each uterine artery and opposite each other, one branch penetrating the anterior and the other the posterior uterine wall. These two pairs of branches, which may be called arcuate arteries on account of their course in the myometrium, divide the uterine wall into a narrow outer or peripheral zone nourished by the peripheral branches of these arteries and a wide, inner or radial zone supplied by their radial branches (so named on account of their course). The latter terminate in the endometrium. The greater portion of the arterial supply of the uterus is directed toward its mucosa (Fig. 1). Each pair of arcuate arteries supplies a segment of the uterus corresponding to a segment of the Müllerian duct of that side.

The venous blood is conveyed from the uterine tissues mainly by the arcuate veins (corresponding in their general course with that of the arcuate arteries) which empty into the uterine plexus of veins, situated between the layers of the broad ligament. The arcuate veins receive blood from both the peripheral and the radial zones of the uterus (Fig. 2). The venous capillaries of the mucosa, some of which are dilated forming sinuses (Fig. 3), empty into the venous sinuses of the radial zone of the myometrium and these in turn into the arcuate veins. Some of the former are relatively large and radiate from the endometrium (Fig. 10). I have named these sinuses radial or, better, receiving sinuses, as they receive the greater portion of the blood from the endometrium and are continuous with the dilated capillaries (sinuses) of the latter. It is obvious that foreign material gaining access to the mucosal sinuses might escape through the receiving sinuses into the deeper vessels of the uterine wall. As there are no valves in the sinuses and veins of the uterine wall, the various physiologic changes in the venous pressure in these vessels might readily force foreign material in them into any of the sinuses and veins of the uterine wall, including those of the peripheral zone (Fig. 11), as they are to one side of the main blood stream which passes through the radial zone into the arcuate veins and thence to the uterine veins between the layers of the broad ligament. Only the principal veins of the uterus have well defined walls; the greater number of them, including the receiving sinuses, are usually only endothelial-lined spaces between the muscle bundles. In the non-injected specimen the veins and venous sinuses are often empty or contain very little blood and are therefore readily taken for lymphatics.

At menstruation some of the capillaries of the mucosa rupture and blood escapes into the tissues of the latter (Figs. 6, 7 and 8). Often bits of the mucosa may be found lying free in this extravasated blood. It is natural to assume that at times some of these bits might escape into the lumen of a ruptured mucosal capillary or sinus and be carried through a receiving sinus into the deeper vessels of the uterine wall. This does occur as will be shown.

The histologic study of the ectopic endometrial tissue in a direct or primary endometriosis (so-called adenomyoma of mucosal origin) shows that this tissue contains venous capillaries (Fig. 12) similar to those of the mucosa lining the uterine cavity (possibly not so

large) and furthermore that this tissue, in its invasion of the myometrium, often extends in the spaces occupied by the vessels and sinuses of the uterine wall but is separated from the lumen of the latter by the endothelial lining of the vessel (Figs. 14, 15, 16, 17 and 18), as has been emphasized by Robert Meyer in his description of the relation of this ectopic endometrial tissue to the lymphatics of the uterine wall. (I believe, however, that the majority of these vessels are veins and not lymphatics.) It might be assumed that in the menstrual reaction of this misplaced endometrial tissue, bits of it might escape into its venous capillaries and also possibly into the lumen of a sinus of the uterine wall along which the endometrial tissue often extends in an extra- or retro-endothelial course. I also believe that the same applies to misplaced endometrial tissue of other origin than from a direct invasion of the uterine wall by its mucosa (Fig. 13). In one instance of an endometriosis of the cul-de-sac presenting in the posterior vaginal vault (a so-called adenomyoma of the recto-vaginal septum) the actual escape of the menstrual contents of two ectopic endometrial cavities into adjacent veins was found (Figs. 60 and 61) and, furthermore, bits of endometrium were present lying free in the lumina of and implanted on the lining of veins about these cavities (Figs. 58, 59 and 66). As a result of this finding I believe that a similar condition occasionally must arise in a direct endometriosis of the uterine wall. I have not definitely demonstrated it after a careful study of many sections from many blocks of tissue from uteri with a direct endometriosis, which were removed during the menstrual period, but believe that either it has been seen by others or will be found.

As bits of the uterine mucosa at times escape into the venous circulation of the uterus during menstruation, certain questions naturally arise. What is its pathologic and clinical significance? Could it possibly give rise to ectopic endometrial tissue not only in the uterine wall but also outside of that organ?

The Lymphatic Circulation of the Uterus

Is it possible for bits of the uterine mucosa to be disseminated through the lymph vessels during menstruation, or may it actually invade these vessels and pieces of it escape through these channels? I have attempted to inject the lymphatics of the uterine wall and its mucosa but failed. Vessels which I have previously considered

lymph vessels have corresponded to the venous capillaries and sinuses of uteri in which the veins have been injected. The subperitoneal lymph vessels about the uterine cornua and between the layers of the broad ligament may often be easily recognized without injecting them; but when one attempts to inject the deeper lymphatics of the uterine wall the venous capillaries and sinuses often become filled with the injection medium and may readily be taken for lymph vessels because they have a structure similar to the latter.

In an article [2] published in 1922, I suggested that endometrial tissue might metastasize through lymph vessels, because I had found an endometrial polyp projecting into the lumen of a lymph vessel situated between the layers of the broad ligament. This polyp had arisen from the invasion of the vessel by endometrial tissue outside of the vessel pushing the endothelial lining of the lymphatic ahead of it. I also added that metastases might arise from the direct invasion of the uterine wall by the mucosa lining its cavity and from a similar invasion of the tubal wall by its mucosa.

In 1924 Halban published a preliminary communication [3] on the metastatic origin of misplaced endometrial tissue through the lymphatics. He believed that in the invasion of the myometrium by its mucosa some of the epithelium escapes into the lymph spaces between the muscle bundles of the uterine wall and is carried through these to the superficial lymphatics beneath the serosa and from there spreads by the lymph channels to other pelvic structures including the inguinal lymph nodes.

The following year I [4] discussed the possibility of metastasis of endometrial tissue through the lymph channels and suggested that the menstrual reaction of endometrial tissue encroaching upon or protruding into a lymphatic might disseminate bits of this tissue into its lumen and lead to metastasis. Robert Meyer, in a letter to me, justly criticised my suggestions and theories because I had not actually proved them. He referred to his own publications [5] and those of Kitai [6] where they had attempted to find evidence that endometrial tissue actually broke through the endothelial lining of the lymph vessels but had been unable to prove that it had. He well describes [7] the relation between the invading endometrial tubules and the lymph vessels and the way the former often follow these vessels and distort them without actually gaining access to the lumen

of the vessel. I can confirm Robert Meyer's observations as to the extra-endothelial course of endometrial tissue accompanying the vessels of the uterine wall in a direct endometriosis, but believe that the latter are usually venous sinuses and not lymph vessels. I also believe that the menstrual reaction of the endometrial tissue alongside of a vessel might cause rupture of the endothelial lining of the vessel and permit bits of endometrial tissue to escape into its lumen, but have not been able definitely to prove it.

Due to my inability to recognize the lymphatics of the uterine mucosa and the deeper tissues of the myometrium I have been unable to determine the part they take in the dissemination of endometrial tissue.

For anatomic and physiologic reasons it seems to me that metastases of endometrial tissue from the uterine mucosa and also from ectopic endometrial foci are more apt to be of venous than of lymphatic distribution. Still, this is a minor point which in time will be settled.

Endometrial Tissue in the Venous Sinuses of the Uterine Wall due to Artefacts

If bits of endometrial tissue sometimes escape into the venous circulation of the uterus during menstruation, they should occasionally be seen in the veins and venous sinuses of uteri removed during the menstrual period. The problem would seem to be a very easy one. If they were not found after a careful study of many sections from many menstruating uteri it probably does not occur and if bits of endometrial tissue are discovered lying free in the lumina of these vessels the problem is solved. I encountered certain technical difficulties. The veins and venous sinuses of the uterus removed by operation are often empty or contain very little blood. The surgeon usually clamps the uterine side of the ovarian and uterine vessels and ligates the distal portion cutting between the clamps and the ligatures. After the uterus has been removed and the clamps released from the vessels the greater portion of the blood within the uterus escapes from the severed vessels and might carry with it any foreign material present in that blood. If the uterus is incised before it is fixed more blood escapes from its tissues. I partially obviated this difficulty by doubly ligating the vessels and

cutting between the ligatures before removing the uterus. The entire specimen was hardened in formalin and blocks were not cut from it until it was fully fixed. The uterus was cut into cross slices and these slices were cut in halves or quarters depending upon their size and embedded in celloidin. The majority of the veins and venous sinuses of the uterine wall were still found to be empty or to contain very little blood, but the uterine plexus of veins on either side of the uterus was distended with blood. During fixation the uterus evidently contracts and forces the greater portion of the blood in its sinuses into the veins on either side of it.

Bits of uterine mucosa were found in the veins and sinuses of the wall of menstruating uteri. A careful study of these sections and the process of embedding showed that some of these findings were due to artefacts. The menstruating uterine mucosa is very friable; bits of it break off during the process of embedding and readily drop into the empty veins and sinuses of the uterine wall. These appear as endometrial emboli in the stained sections (see Figs. 19, 20 and 21). If, however, pieces of the uterine mucosa are found surrounded by blood in a vein or sinus or attached to the wall of the vessel by fibrin, it is evident that they reached this situation before the tissues were fixed. It is also possible that bits of the uterine mucosa may be carried into the venous sinuses of the uterine wall in cutting blocks from the unfixed uterus.

Endometrial Tissue in the Veins and Venous Sinuses of the Uterine Wall Due to the Menstrual Dissemination of this Tissue into these Vessels

Fragments of endometrial tissue were found either in the blood of the veins and venous sinuses of the uterine wall or attached to the lining of these vessels by fibrin in three uteri removed during the menstrual period (Cases 1, 3 and 4). In two other uteri, removed during the menstrual period, clumps of epithelium-like cells which I was unable to identify, were found in the blood or attached to the walls of veins. A careful study of three other uteri removed during menstruation failed to reveal any embolic endometrial tissue in the vessels of the uterine wall but several artefacts were present in sections from one uterus (see Figs. 19*a*, 20 and 21). Sections were carefully examined for endometrial tissue in the veins and venous

sinuses of many uteri removed at other times than during menstruation, and embolus-like lesions of endometrial tissue were found in only one uterus (see Case 2).

The histologic findings in four cases are reported, demonstrating the possible significance of the menstrual dissemination of bits of the uterine mucosa into the venous circulation of the uterus.

CASE 1. Patient aged 32, single. Uterus and right tube and ovary removed March 21, 1925, for a large submucous myoma on the second day of the menstrual period. Pieces of uterine mucosa were found in the blood of a mucosal sinus (Fig. 22), in a receiving sinus of the myometrium (Fig. 24), and also in other veins of the uterine wall (Fig. 25). A mural thrombus containing similar fragments was present in one of these veins (Fig. 26). The "endometrial tissue" in this thrombus stained poorly as compared not only with the uterine mucosa but also with the pieces of the latter found in the lumina of the other vessels of the same specimen (Figs. 27*a* and 27*b*), thus suggesting that they were undergoing degenerative changes and had been separated from the uterine mucosa for a longer time than the latter. There was associated an endometrial cyst of the right ovary which was fused with the posterior layer of the broad ligament, apparently resulting from a previous rupture or perforation of the cyst. The endometrial lining of the cyst showed the same menstrual reaction as that of the uterine cavity. Multiple lesions containing endometrial tissue involved the peritoneum about the right ovary and also were present in the posterior cul-de-sac. The distribution of these lesions was such as to indicate their origin from the escape of the contents of the endometrial cyst of the ovary into the peritoneal cavity.

CASE 2. Patient aged 33, single. Uterus and both tubes and ovaries removed Nov. 20, 1924, three weeks after the last menstrual period, for an extensive peritoneal endometriosis associated with bilateral ovarian cysts of endometrial type. The posterior wall of the uterus was deeply invaded by endometrial tissue apparently developing on its peritoneal surface or at least in the peripheral zone of the uterus. Endometrial emboli were found in four veins of the uterine wall, all of them either arcuate veins or their peripheral branches. The histologic relation of these emboli to the contents of the veins and their lining was such as to lead one to believe that they could not be artefacts (Figs. 28 and 29). Most of the endometrial

tissue in these vessels, both epithelium and stroma, stained poorly as compared with the mucosa lining the uterine cavity, suggesting degenerative changes. I believe that they might have escaped into the venous circulation of the uterus during menstruation. The last flow occurred three weeks before the operation.

CASE 3. Patient aged 53, single. Uterus and both tubes and ovaries removed April 10, 1926, for an endometriosis of its anterior wall, apparently of the direct type (Figs. 14, 15, 16, 17 and 18). Patient had been flowing for five weeks prior to the operation. A gland-like arrangement of "uterine epithelium" was found attached by fibrin to the wall of a receiving sinus (Figs. 32 and 34), thus demonstrating that it must have reached this situation before the tissues had been fixed. In another receiving sinus a polypoid growth of endometrial tissue, apparently covered by endothelium and consisting of a typical uterine gland surrounded by stroma,was attached by a slender pedicle to its wall (Figs. 30, 31 and 33). While an endometriosis of the uterine wall involved the tissues about a branch of this sinus at another level of the block, serial sections showed that the gland of the polyp was not continuous with any endometrial tubule outside of the sinus. (In all cases where I have been able to obtain either serial sections or many sections of polypoid invaginations of endometrial tissues into vessels, it was possible to demonstrate that the apparent gland-like structure in the polyp was but a section of an epithelial tubule continuous with those outside of the vessel (see Figs. 14 to 18 inclusive).) The endometrial polyp in this case must have arisen either from (1) a metaplasia of the endothelial lining of the sinus, (2) an implantation of a fragment of endometrial tissue escaping into the sinus from the uterine mucosa during menstruation, (3) an implantation of a piece of endometrial tissue escaping into a branch of the sinus during the menstrual reaction of the heterotopic endometrial tissue about it, or (4) if it previously had been continuous with the endometrial tissue about a branch of the sinus (at another level), this connection in some way must have been severed.

Another interesting problem presents itself in this case and that is whether or not some of the ectopic endometrial tissue of the uterine wall may have been of metastatic or embolic origin rather than arising from the direct invasion of the myometrium by its mucosa. The uterine epithelium adherent to the wall of a sinus, the polyp

and other findings in the case strongly suggested this possibility (see Figs. 33, 34 and 35).

CASE 4. Patient aged 41, married; one child 14 years old. Uterus, both tubes and ovaries removed March 9, 1926, on the second day of the menstrual period, for a peritoneal endometriosis fusing the anterior surface of the uterus with the bladder, with partial obliteration of the anterior cul-de-sac; a similar lesion obliterating the bottom of the posterior cul-de-sac, with invasion of the sigmoid causing partial intestinal obstruction, and extension downward between the rectum and the vagina and into the posterior vaginal vault. Following the suggestion of Dr. William P. Graves [8] a temporary colostomy was made which later closed spontaneously.

Ovaries were normal and tubes were patent. An endometriosis, in many ways displaying the histologic structure of the direct type, was present in the left half of the posterior uterine wall (Figs. 36, 38 and 39) with but slight invasion of the right half of the posterior uterine wall and that near the fundus. In the right half of the posterior uterine wall endometrial emboli were lying free in the lumina of some of the veins of the peripheral zone (Figs. 37, 43, 53 and 65). Multiple embolic or metastatic growths of endometrial tissue were found in the arcuate veins and also in the peripheral veins of that side (Figs. 37, 49 and 52). Serial sections showed that these deposits of endometrial tissue were attached to the walls or lining of these vessels and were not continuous with any endometrial tissue outside of the vessel. They were evidently due to a localized metaplasia of the endothelial lining of the vessels or an implantation (anchoring) of bits of endometrial tissue similar to those which were found floating about in the lumina of some of them. The study of the specimen suggested that they primarily arose from the menstrual dissemination of fragments of endometrial tissue from the uterine mucosa into receiving sinuses rather than from the menstrual reaction of the ectopic endometrial tissue in the left half of the posterior uterine wall. In only a very few areas of ectopic endometrial tissue of the left half of the posterior uterine wall was there any suggestion of a menstrual reaction (Fig. 40). Had these emboli arisen from this source, one would have expected to have found more of them in the sinuses and veins of that half of the uterus rather than in those of the opposite side. As it was, only a very few were found in the left half of the posterior uterine wall and those in the peripheral zone

(Fig. 41), while many were found in the veins and venous sinuses of the opposite side. A bit of endometrial tissue was found in a sinus of the uterine mucosa (Fig. 55) and also embolic lesions were found in the receiving sinuses of the right half of the posterior uterine wall (Figs. 53 and 54), thus suggesting that it was through such channels that the endometrial tissue had primarily escaped in order to reach the arcuate and peripheral veins of the side in which the embolic lesions were most numerous. It seems reasonable to believe that these endometrial vegetations in the sinuses and veins arose from the anchoring or implantation of endometrial fragments similar to those found floating in these vessels and were primarily derived from the menstrual dissemination of endometrial tissue from the uterine mucosa into the venous circulation of the uterus. On the other hand, some of the endometrial tissue floating in these vessels might be pieces cast off by a menstrual reaction in the embolic vegetations of endometrium growing on their walls.

A peritoneal endometriosis was present in the anterior cul-de-sac fusing the anterior surface of the uterus with the anterior layer of the broad ligament and the peritoneum covering the bladder and apparently arising by peritoneal implantation (Fig. 56). Only the peripheral zone of the anterior uterine wall was invaded by this tissue and no deeper than the corresponding invasion of the anterior layer of the broad ligament and the peritoneum covering the bladder. The entire uterine wall was cut into blocks and many sections were studied from each block. Endometrial tissue was not found in the deeper portions of the anterior uterine wall. Could the endometriosis in this situation possibly have arisen from metastasis to the peripheral vessels of the anterior uterine wall, similar to that already described, and later extending to the peritoneal surface? Such an origin cannot be excluded. Had it been metastatic through veins or lymphatics we would expect to find in it emboli similar to those of the right half of the posterior uterine wall but none was found. In a few places, however, a possible communication of the endometrial tissue with the lumen of a sinus was found where portions of the endometrial tissue were definitely intra- and not retro-endothelial, thus suggesting a possible metastatic origin. It is also possible that the extensive endometriosis of the radial zone of the left half of the posterior uterine wall was of metastatic rather than of direct origin as in only one place was an invasion of the uterine

wall by its mucosa found and that apparently for only a short distance. Its continuation with the extensive endometrial lesions of that wall was not definitely established. The distribution of the endometrial tissue in this portion of the posterior uterine wall (Fig. 36) conformed with the distribution of the bismuth in corresponding sections of the walls of uteri in which the veins had been injected. The endometrial tissue in this lesion was nearly everywhere of the direct type, *i. e.*, wherever the lumen of a vein or sinus could be seen the endometrial tissue was retro- and not intra-endothelial, except in a few areas (where it possibly communicated with the lumen of a vein) such as were present in the peripheral zone. I believe that a metastatic lesion may possibly become entirely retro-endothelial by the growth of the endothelial lining of the vessel over it, as endothelium grows over a thrombus, and subsequently it may take a retro-endothelial course in its extension and thus be histologically indistinguishable from the lesion of a direct endometriosis. In several of the embolic lesions the endothelium of the vein or sinus had grown over portions of the endometrial implant (see Figs. 41, 50 and 52) so as to suggest that it might completely cover it, although nowhere was this conclusively shown.

The posterior surface of the body of the uterus was not adherent but the bottom of the posterior cul-de-sac was occluded by an extensive endometriosis fusing the posterior wall of the cervix with the recto-sigmoid. The nature of the intestinal lesion was not ascertained as the sigmoid was not resected.

The endometriosis of the portion of the posterior vaginal wall, which was excised, was as interesting as that of the uterus. Multiple ectopic endometrial cavities were found filled with blood in which were floating bits of endometrial tissue (Figs. 57, 58 and 60). Similar fragments were found lying free in the lumina of nearby veins and also anchored to or implanted on the walls of veins (Figs. 58, 59 and 66). The actual escape into a vein of the menstrual contents of two of these endometrial cavities could be demonstrated (Figs. 60 and 61). Here again we have evidence that endometrial tissue may be disseminated into veins during menstruation and actually become implanted on the walls of veins, thus demonstrating that the fragments of endometrium set free by the menstrual reaction are sometimes alive and capable of becoming implanted under favorable conditions.

What was the origin of the ectopic endometrial tissue in this case? I have proved that some of the lesions were of mestastatic or embolic origin and also was able to find a direct invasion of the uterine wall by its mucosa. It was not possible, however, to determine whether or not the latter gave rise to all of the endometrial tissue in the extensive endometriosis of that portion of the uterine wall. It was also shown that there were peritoneal lesions of implantation type, possibly due to the escape of menstrual blood through the tubes into the peritoneal cavity. The tubes were patent and endometrial tissue was not found in the ovaries. If one method for the extension or dissemination of endometrial tissue was primarily responsible for the endometriosis in this case, we must choose the metastatic (embolic), *i. e.*, the menstrual dissemination of bits of the uterine mucosa into the venous circulation of the uterus. Some of the tissue emboli might have become retro-endothelial and in their subsequent extension caused the endometriosis of the radial zone of the left half of the posterior uterine wall in which the distribution of endometrial tissue simulated that of the bismuth in the uterine wall whose veins had been injected and were of the type of a direct endometriosis. Metastases in the subperitoneal veins of the uterine walls might have subsequently extended through to the peritoneal surface causing a peritoneal endometriosis with a later extension to the peritoneum covering the bladder in the anterior cul-de-sac and the sigmoid and recto-vaginal septum in the posterior cul-de-sac. I admit the possibility of the above but am inclined to believe that there was more than one method of origin of the ectopic endometrial tissue in this case.

The Bearing of these Studies on the Etiology of Other Varieties of Endometriosis than those Just Described

If fragments of endometrial tissue escape into the venous circulation of the uterine wall during menstruation and become implanted on the endothelial surface of the veins and venous sinuses of that organ and if a similar condition arises in veins about misplaced endometrial cavities in the vagina, it is natural to assume that a like implantation of this tissue might occur in veins remote from these endometrial cavities. This might account for the origin of misplaced endometrial tissue at a distance from the uterus, such as

some of those in the vagina, vulva, groin, or even the umbilicus, the latter through the round ligament and epigastric veins.

If menstrual blood carrying with it bits of endometrial tissue escapes into the venous circulation of the uterus and these bits sometimes become implanted on the endothelial surface of the veins and venous sinuses of the uterine wall, and if a like condition arises from the menstrual reaction of the mucosa of ectopic endometrial cavities in the vagina, we might infer that bits of endometrial tissue carried by menstrual blood escaping into the peritoneal cavity from any source (such as a back flow through the tubes from the uterine cavity, from the rupture or perforation of an endometrial cyst of the ovary or the menstrual reaction of endometrial tissue on the surface of the various pelvic structures) might become implanted on the mesothelial surface of the peritoneum and give rise to at least some of the lesions of peritoneal endometriosis. Jacobson has shown by his experimental work in rabbits and monkeys that bits of the uterine mucosa of these animals, scattered in their peritoneal cavities, become implanted on the peritoneum causing a peritoneal endometriosis similar to that found in human beings. The findings in the cases just reported demonstrate that bits of endometrial tissue disseminated by menstruation are sometimes alive and can become implanted on the endothelial lining of veins and venous sinuses. We know that menstrual blood, containing bits of endometrium, at times escapes into the peritoneal cavity from the above mentioned sources. Peritoneal endometriosis in women often occurs in situations and under conditions indicating (or at least suggesting) its origin from these sources.

The Origin of Endometrial Tissue in Uterine Endometriosis

The study of endometriosis of the uterine wall demonstrates that it may arise in four, and possibly more, ways.

1. The direct invasion of the uterine wall by its mucosa or by tubal mucosa — a direct or primary uterine endometriosis.
2. The invasion of the external portion of the uterine wall by the direct extension of endometrial tissue from an ectopic endometrial focus in the pelvis — an indirect or secondary uterine endometriosis, by extension.

3. From endometrial tissue implanted or developing on its peritoneal surface — an implantation or peritoneal uterine endometriosis.
4. From the menstrual dissemination of endometrial tissue into the venous circulation of the uterus, either from the mucosa lining its cavity or from ectopic endometrial tissue in the myometrium — an embolic or metastatic uterine endometriosis.
5. The possibility of metastasis through the lymphatics, and also of developmental inclusions of the uterine mucosa in the myometrium, must be considered. The origin of endometrial tissue from a metaplasia of the endothelial lining of vessels does not appeal to me.

Summary

A histologic study was made of sections of uteri removed during the various stages of the menstrual cycle, in which the veins had been injected with bismuth. By this means it was demonstrated that there are venous capillaries and large venous sinuses in the uterine mucosa and that the latter empty into similar sinuses (receiving) in the uterine wall. During menstruation, blood escapes from the mucosal vessels into the surrounding tissues, and bits of the mucosa are often set free in the extravasated blood. These studies suggest that this menstrual blood containing fragments of endometrial tissue, at times escapes through a ruptured mucosal sinus into the venous circulation of the uterus.

Sections of misplaced endometrial tissue, wherever situated and irrespective of its origin, also suggest that a like dissemination of fragments of this tissue occurs during menstruation.

In menstruating uteri bits of the uterine mucosa at times actually escape into the venous circulation of the uterus through these channels. I have not been able definitely to prove this in a direct endometriosis of the uterine wall but believe that it also must occur in this condition. The escape into veins of the contents of two ectopic endometrial cavities was found in an endometriosis of the posterior vaginal wall.

In one uterus removed during menstruation (Case 4) in which bits of endometrial tissue were found in the blood in veins and venous sinuses of the uterine wall, multiple embolic or metastatic-like growths of endometrial tissue also were present in these vessels.

By serial sections it was shown that these growths either arose from or were implanted on the walls or linings of these vessels and did not arise from the invasion of the latter by endometrial tissue from without. These embolus-like growths of endometrial tissue must have originated either from a localized metaplasia of the endothelial lining of the veins and venous sinuses or else from the actual anchoring and implantation of endometrial tissue similar to that found free in some of the vessels of the specimen. The study of the entire uterus demonstrated that, while some of the endometrial emboli lying free in the vessels of the uterine wall might have arisen from the menstruation of ectopic endometrial tissue in that organ, the latter primarily were derived from the mucosa lining the uterine cavity. In the endometriosis of the posterior vaginal wall of this case, similar endometrial emboli and embolic vegetations of endometrial tissue were present there in veins about misplaced endometrial cavities and the actual escape of the menstrual contents of two of these cavities into a vein was seen.

In a second uterus, also removed while the patient was flowing (Case 3), somewhat similar lesions were found in which their embolic origin was not as definitely established as in Case 4. Nevertheless I believe that they had a similar origin.

If these observations are correctly interpreted, they show that bits of endometrial tissue disseminated by menstruation from the mucosa lining the uterine cavity and also from ectopic endometrial foci, are not always dead but are sometimes alive and are capable of becoming implanted on the endothelial surface of nearby veins and venous sinuses.

They further suggest that bits of endometrial tissue carried by menstrual blood into the venous circulation might cause metastatic growths of endometrial tissue at a distance from the original focus, and also that similar fragments of endometrial tissue carried by menstrual blood escaping from any source into the peritoneal cavity at times might cause the lesions of peritoneal endometriosis.

Conclusions

1. Fragments of endometrial tissue, at times, are disseminated into the venous circulation during menstruation, from the mucosa lining the uterine cavity and also from ectopic endometrial foci.

2. Metastatic or embolic endometriosis arises from the implantation of these emboli in nearby veins.

3. Endometrial tissue set free by menstruation, therefore, is sometimes not only alive but may actually continue to grow if transferred to situations favorable to its existence.

The colored illustrations for this paper were made by Mrs. M. R. Marden and the photomicrographs by Mr. James A. Glenn.

The demonstration of the origin and course of the ectopic endometrial tissue in these specimens was made possible by the technical skill and care of Miss Isabel Peck.

These I thank for their interest and coöperation.

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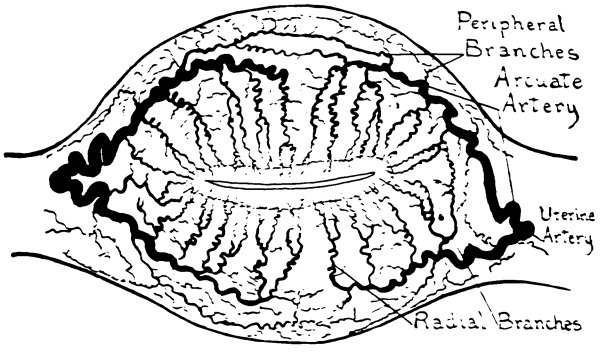
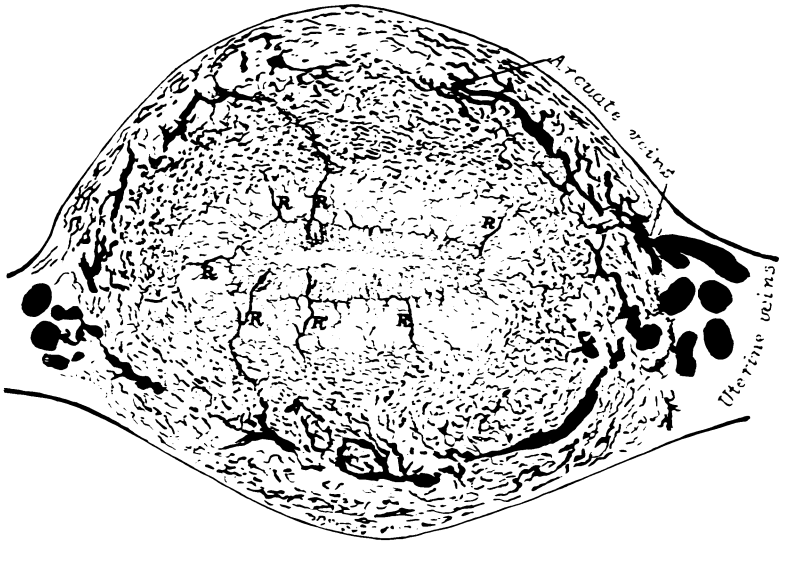
PLATE 20

FIG. 1. The general plan of the distribution of the intrinsic uterine arteries as seen in a cross-section of the body of the uterus. Composite tracing (slightly enlarged) of roentgenograms of thin cross slices of the uterus; arteries injected with bismuth. The arcuate arteries, which arise in pairs from each uterine artery, divide the uterine wall into a narrow outer or peripheral zone nourished by the peripheral branches of these arteries and a wide inner or radial zone supplied by their radial branches. The latter terminate in the mucosa. The greater portion of the arterial supply of the uterus is directed toward its mucosa.

FIG. 2. The general plan of the venous outlets of the uterine tissues as seen in a cross-section of the body of the uterus. Tracing (enlarged and with some of the receiving sinuses accentuated) of a roentgenogram of a thin cross slice of the uterus, veins injected with bismuth; hyperemia due to tubal pregnancy. The venous blood is conveyed from the uterine tissues mainly by the arcuate veins which empty into the uterine plexus of veins situated between the layers of the broad ligament. The arcuate veins receive blood from both the peripheral and the radial zones of the uterus. The venous capillaries of the mucosa, some of which are dilated forming sinuses (Fig. 3), empty into the venous sinuses of the radial zone of the myometrium and these in turn into the arcuate veins. Some of these sinuses are relatively large and radiate from the endometrium (R of illustration). It is obvious that foreign material gaining access to the lumina of the mucosal sinuses might escape through the radial or receiving sinuses (R) into the deeper sinuses and veins of the uterine wall.


Peripheral
Branches
Arcuate
Artery
Uterine
Artery
Radial Branches

1


Arcuate veins
Uterine veins

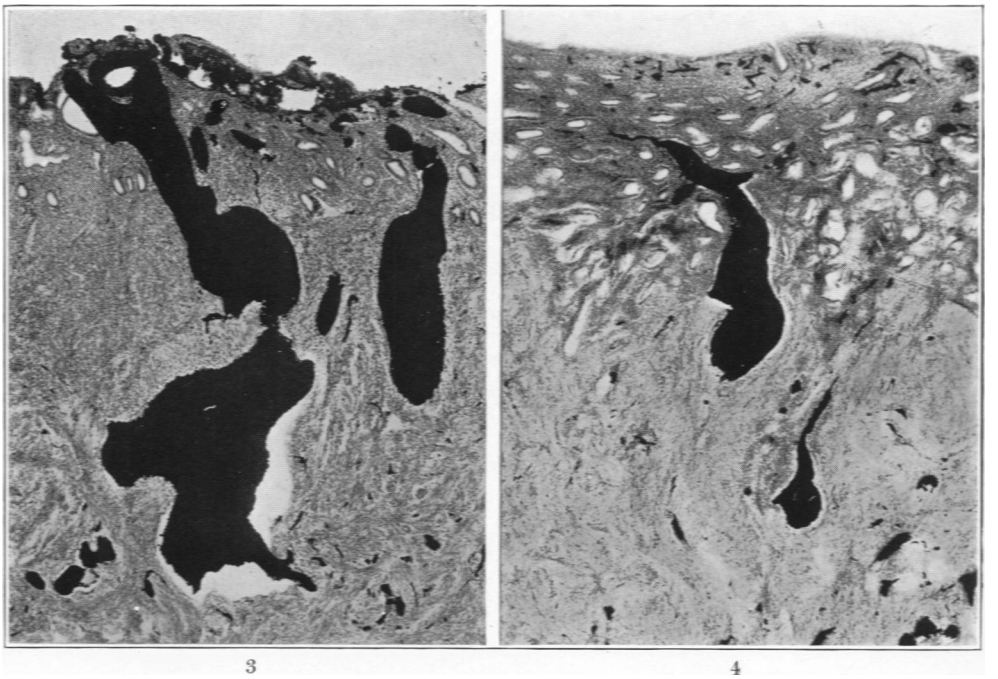
2

PLATE 21

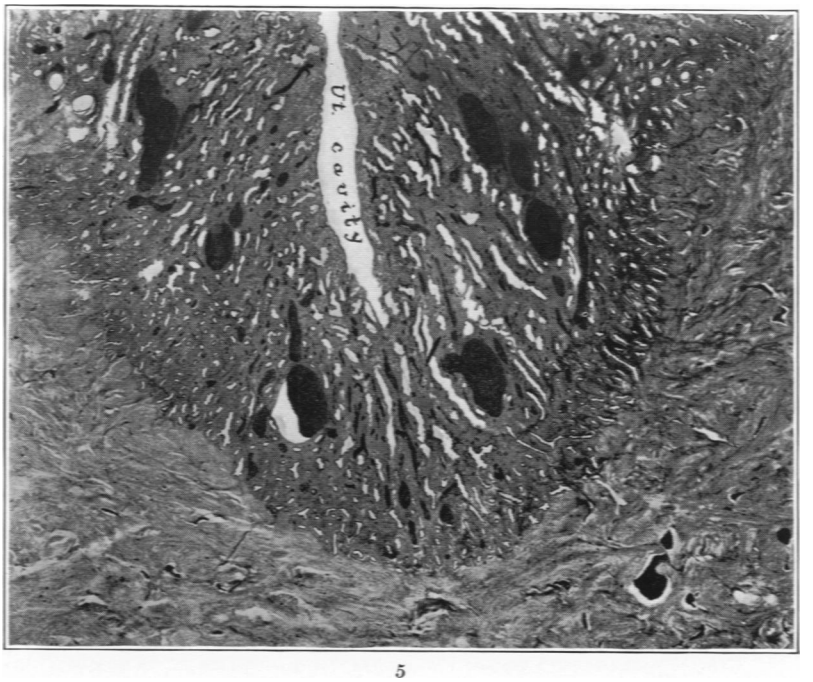
FIG. 3. Photomicrograph (× 25) of a section of the uterine mucosa and underlying muscularis, veins injected with bismuth; from a patient with tubal pregnancy. Condition present corresponds with that found at the close of the menstrual period. Two receiving sinuses are shown, one of which extends almost to the surface of the uterine mucosa. The portion of the sinus situated within the mucosa might be designated a mucosal sinus. These sinuses are but spaces lined by endothelium and without definite walls. In the non-injected specimen they are often empty or contain very little blood and therefore could readily be mistaken for lymph vessels. Any foreign material in the lumen of the mucosal sinus might easily escape into the receiving sinus of the muscularis with which it is continuous.

FIG. 4. Photomicrograph (× 25) of a section of the uterine mucosa and underlying muscularis, veins injected with bismuth; interval stage of the menstrual cycle. The mucosa is about twice as thick as that shown in Fig 3. A receiving sinus is present and due to the postmenstrual growth of the mucosa, the sinus is more deeply situated than those shown in Fig. 3.

FIG. 5. Photomicrograph (× 10) of a section of the uterine mucosa and underlying muscularis in the angle between the anterior and posterior uterine wall, veins injected with bismuth; premenstrual stage of the menstrual cycle. The mucosa is much thicker than that shown in Fig. 4 (less than half the magnification). Several dilated capillaries or mucosal sinuses are present. As the principal menstrual reaction usually occurs in the superficial portion of the mucosa, could bits of the latter escape into these sinuses during menstruation?



3 4



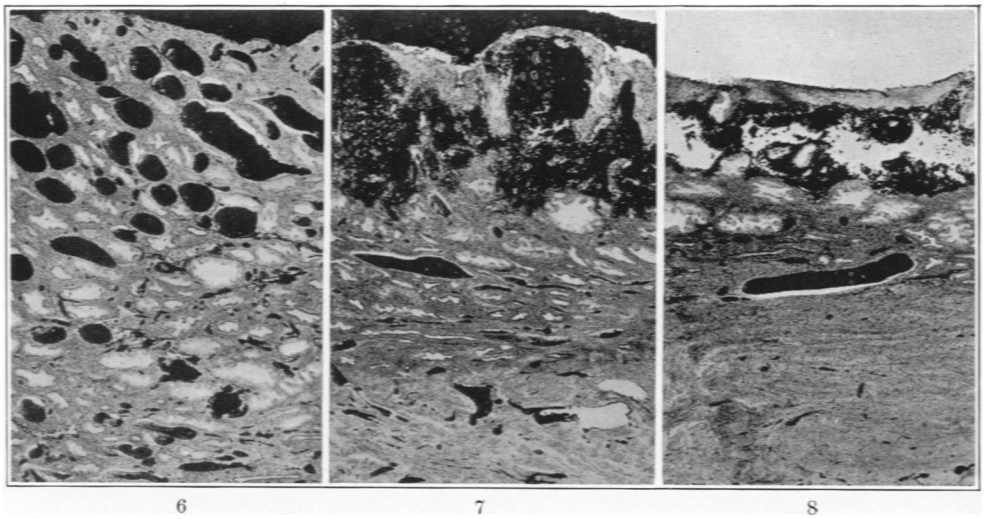
5

PLATE 22

FIGS. 6, 7 and 8. Three photomicrographs (× 20) of sections of the uterine mucosa and underlying muscularis, veins injected with bismuth; patient menstruating. All sections from the same uterus but from different portions and showing different stages in the menstrual reaction. The photomicrograph to the left shows the dilated mucosal capillaries, the middle one the rupture of the same, due to the menstrual reaction, thus permitting the injection mass to escape into the tissues of the mucosa. Fig. 7 represents a still later stage of the menstrual reaction. The superficial layer of the uterine mucosa has been separated from the deeper layer by the extravasated injection mass and bits of the uterine mucosa lie free in this mass just as they are found in the extravasated blood of the non-injected menstruating endometrium. Could menstrual blood carrying with it bits of the mucosa escape into the ruptured dilated venous capillaries and from these into the venous circulation of the uterus?

FIG. 9. Photomicrograph (× 25) of a section of the uterine mucosa and underlying muscularis, veins injected with bismuth; end of the first day of the menstrual period. A mucosal sinus is shown with rupture of its endothelial lining permitting the injection mass to escape into the tissues of the mucosa. It is conceivable that fragments of the uterine mucosa set free by the extravasated blood, might at times escape into the lumen of such a sinus and be carried with that blood into the venous circulation of the uterus (see Fig. 10).

FIG. 10. Photomicrograph (× 5) of a cross-section of the uterine wall including its mucosa (section from which the photomicrograph shown in Fig. 9 was made). The mucosal sinus (M.S.) of the endometrium, which has ruptured, is shown and also a receiving sinus which carries the venous blood from the mucosa. (It is not evident that the mucosal sinus in this photomicrograph empties into this receiving sinus but either it does, or else into one like it.) Blood carrying with it any material, such as bits of the uterine mucosa, which had escaped into the lumen of a mucosal sinus, might readily be carried through a receiving sinus into any of the venous sinuses of the uterine wall and especially into the arcuate veins as the main blood stream is from the mucosa through the receiving sinuses into these veins.



6 7 8

9

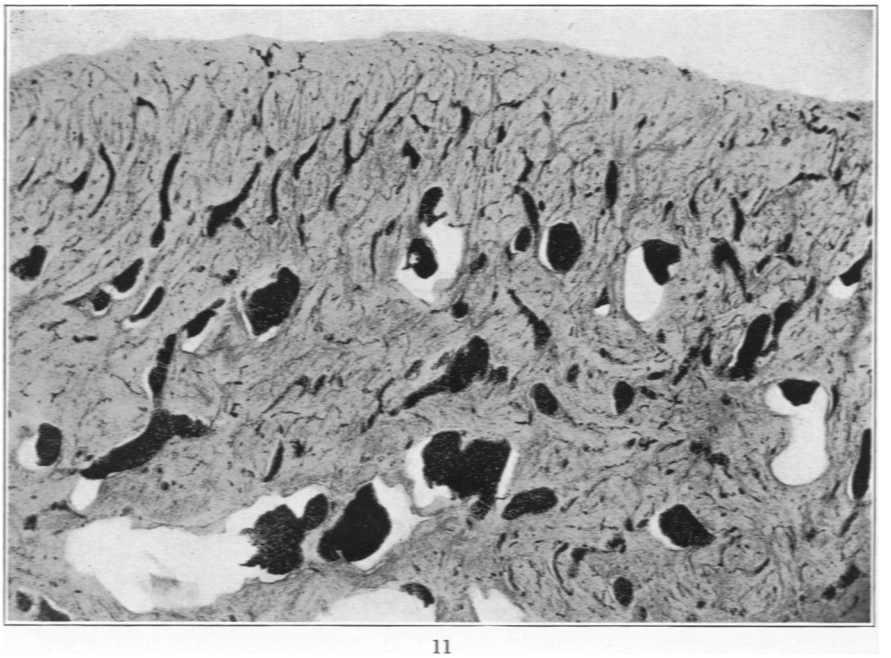
10

PLATE 23

FIG. 11. Photomicrograph (× 25) of a cross-section of the peripheral zone of the uterine wall, veins injected with bismuth; premenstrual stage of the menstrual cycle. The veins and venous sinuses in this section are but spaces, between the muscle bundles, lined by endothelium. They empty into the arcuate veins, bottom of the photomicrograph. (Some of the injection mass has fallen out of the larger vessels.) In the non-injected specimen these vessels are often empty or contain very little blood and may readily be taken for lymphatics. There are no valves in the veins and venous sinuses of the uterine wall. The various physiologic changes in the venous pressure in these vessels, due to uterine relaxation and contraction, might force foreign material suspended in the blood into any of the veins and sinuses of the uterine wall including those of the peripheral zone, since they are to one side of the main blood stream from the mucosa to the arcuate veins, and thence to the uterine veins. For physiologic reasons we might expect to find bits of the uterine mucosa, escaping into the venous circulation, in the vessels of the peripheral zone, even in the small vessels near the serosa where they might be retained.

FIG. 12. Photomicrograph (× 25) of a section of the uterine wall with a direct or primary endometriosis (adenomyoma due to the invasion of the uterine wall by its mucosa), veins injected with bismuth. Dilated venous capillaries (sinuses) are present in this misplaced uterine mucosa similar to those of the mucosa lining the uterine cavity. In the menstrual reaction of misplaced endometrial tissue, fragments of it are set free in extravasated blood just as they are set free in the extravasated blood of the menstruating mucosa lining the uterine cavity. Could some of these bits gain access to the lumina of its venous sinuses and be carried into the venous circulation of the uterine wall? I have examined many sections of primary endometriosis in uteri removed during menstruation, and have not been able to prove that this occurs. I believe that it must occur and will be definitely proved.

FIG. 13. Photomicrograph (× 25) of a section of the uterine wall with an endometriosis near its serosa; veins injected with bismuth. The patient had bilateral ovarian hematomas of endometrial type associated with a peritoneal endometriosis. The misplaced endometrial tissue in this section also contains dilated venous capillaries or sinuses. In the menstrual reaction of this misplaced "uterine mucosa" bits of the latter might also gain access to the lumina of its sinuses.



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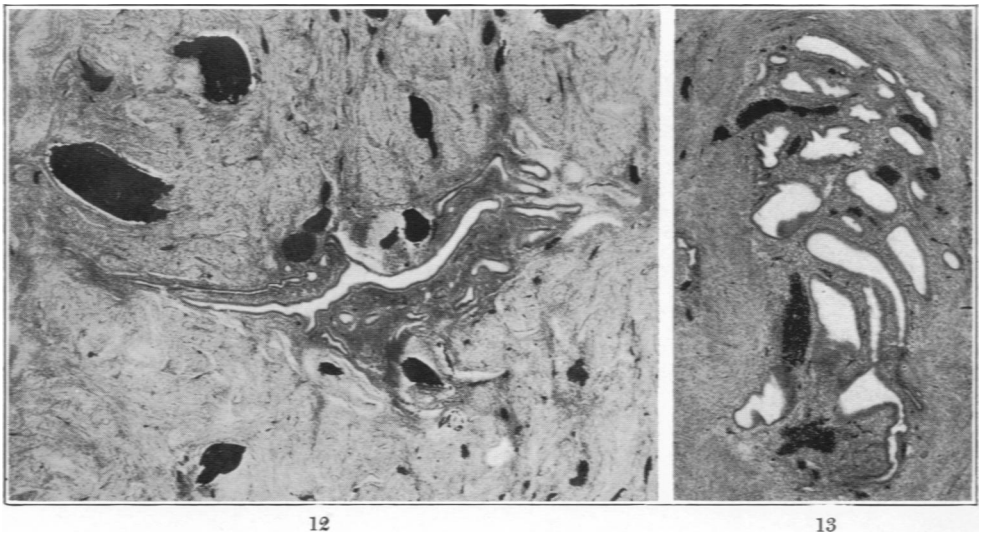


12 13

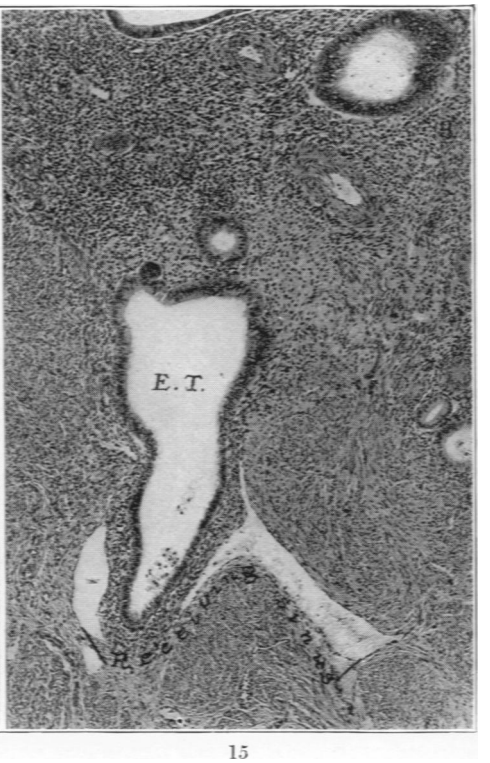
PLATE 24

FIGS. 14 and 15. Two photomicrographs (× 60) of sections from a series showing the invagination of the endometrial tissue of a direct or primary endometriosis into the lumen of a receiving sinus of the uterine wall (Case 3). The first section shows the relation of the endometrial tubule (E.T.) to a receiving sinus (the latter is not a lymph vessel as it contains a small amount of blood and corresponds in its structure and situation with the receiving sinuses of injected specimens). In the second photomicrograph the same endometrial tubule surrounded by stroma is shown bulging into the lumen of the sinus but covered by the endothelial lining.

FIGS. 16, 17 and 18. Three photomicrographs (× 60) of sections from the same series as those shown in Figs. 14 and 15. The first shows a greater bulging of the tubule (E.T.) into the sinus (compare with Fig. 15). In the second one the tubule lies apparently almost entirely within the lumen of the sinus and without any evidence of the endometrial tissue from which it came. The third photomicrograph shows a cross-section of the tubule surrounded by stroma and covered by endothelium and attached to wall of the sinus by the latter. The tubule surrounded by its stroma is apparently within the lumen of the vessel but is extra- or retro-endothelial and not truly intravascular; its epithelium and stroma are directly continuous with the tubule shown in Figs. 14 and 15. The latter was possibly continuous with a tubule of the mucosa lining the uterine cavity. The endometrial tissue within the sinus is not of metastatic or embolic origin because serial sections showed that both the epithelium and stroma are continuous with similar endometrial tissue outside of the sinus (compare with Figs. 30, 31 and 33 from the same case).


E. T.
Receiving Sinus

14


E. T.
Receiving Sinus

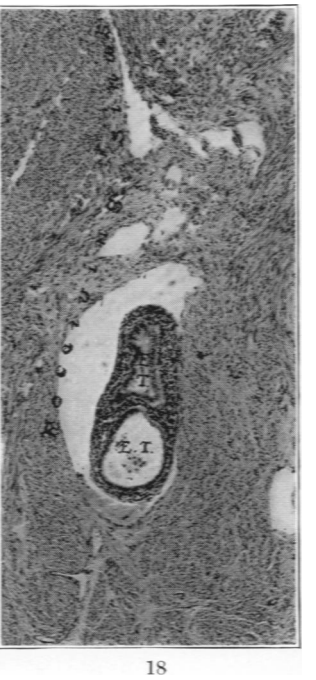
15


E. T.
Receiving Sinus

16


Receiving Sinus
E. T.
E. T.

17


E. T.

18

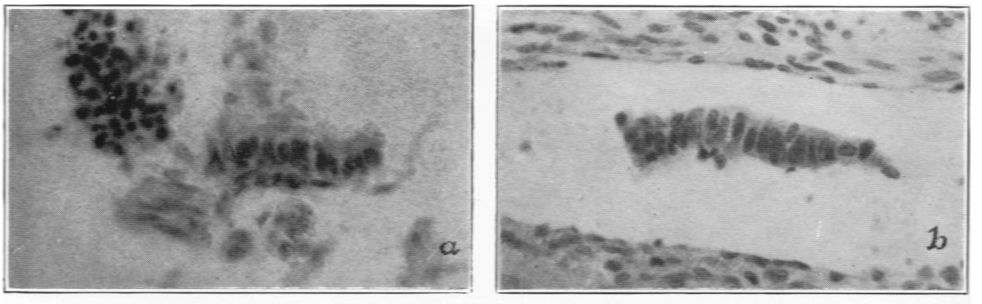
PLATE 25

FIG. 19*a*. Photomicrograph (× 310) of the parametrium with bits of the uterine mucosa (stroma and epithelium) enmeshed in the tissues of the former. The block of the uterine wall from which the section was made included a portion of the uterine mucosa (menstruating). Bits of the friable uterine mucosa were probably set free in the embedding solutions and some of these became entangled in the loose tissues of the parametrium. Similar pieces of the uterine mucosa, in like manner, might fall into a gaping uterine sinus or vein (see Figs. 19*b*, 20 and 21).

FIG. 19*b*. Photomicrograph (× 310) of a receiving sinus of a uterine wall showing a strip of "mucosal epithelium" lying free in its lumen; patient menstruating at the time of the operation. The block of the uterus from which the section was made included a portion of the uterine mucosa. Serial sections had been made and the epithelium was not attached to the wall of the sinus. While I cannot exclude its origin from the menstrual dissemination of this bit of the uterine mucosa into the sinus, I believe that it is more apt to be an artefact and that it arose in the same manner as the fragments of mucosa shown in Fig. 19*a*. Had the epithelium gained access to the sinus before the specimen had been fixed I would expect to find it attached to the wall of the sinus or else with blood about it (see Figs. 25, 27 and 53).

FIG. 20. Photomicrograph (× 310) of a portion of a vein of the uterine wall showing a piece of the uterine mucosa lying free in its lumen; from the same uterus as that shown in Fig. 19*a*; section taken near the surface of another block. I cannot exclude the origin of this tissue from the menstrual dissemination of bits of the uterine mucosa into the venous circulation of the uterus, but for the reasons given in the legend of Fig. 19*b* I believe that it also is more apt to be an artefact.

FIG. 21. Photomicrograph (× 60) of a section of an arcuate vein containing both blood and a bit of the uterine mucosa, the latter lying free in the lumen of the vein, from the same uterus as those shown in Figs. 19*a* and 20 but from a different block of the uterus and from a section taken near the middle of the block. The lumen of the vein is over half filled with blood but the tissue lies free in the empty portion of the vein. It is much more difficult to decide the origin of this bit of tissue. I believe that it also is more apt to be an artefact. A piece of uterine mucosa could drop into the lumen of the unfilled portion of a vein as easily as into an empty one. Had the tissue been embolic from the menstrual reaction it would probably either be partially or wholly embedded in the blood or attached to the lining of the vessels as those shown in Figs. 34, 43 and 53.



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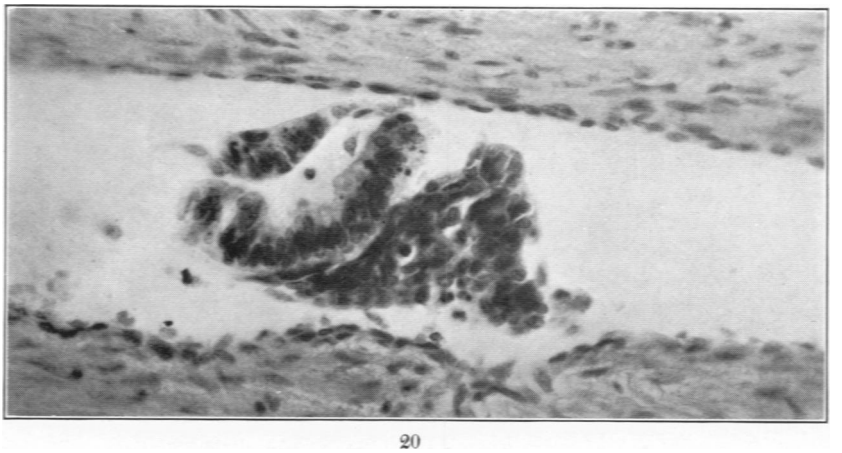

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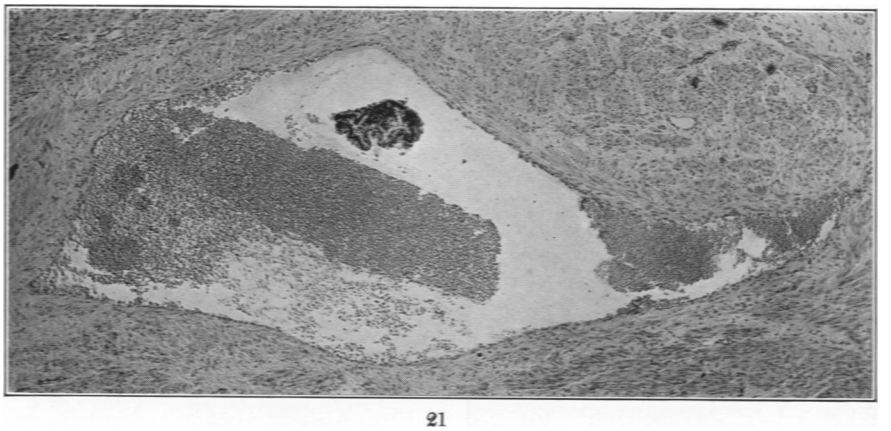

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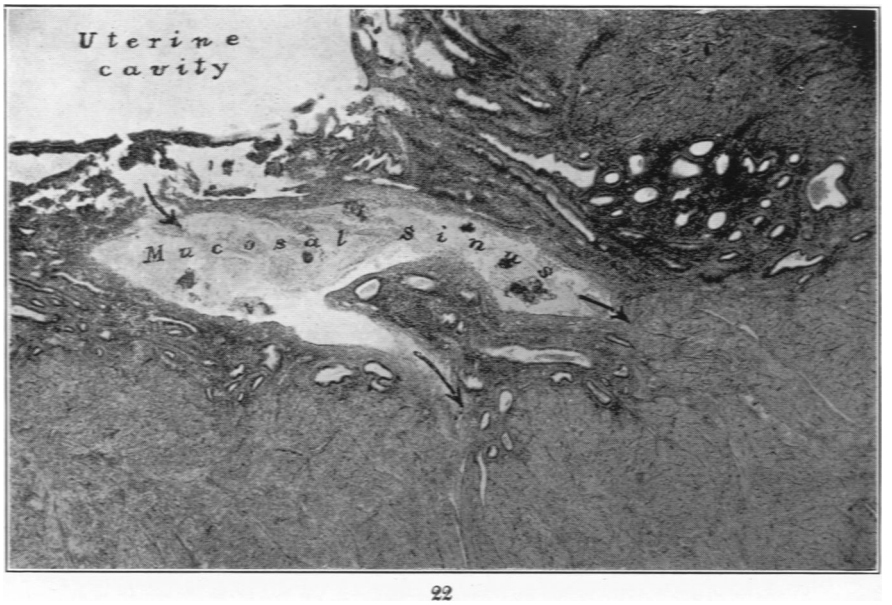
PLATE 26

FIG. 22. Photomicrograph (× 25) of the uterine mucosa and underlying muscularis (in the angle between the anterior and posterior uterine wall) showing blood and bits of the uterine mucosa in a large mucosal sinus; second day of the menstrual period (Case 1). The mucosal sinus is unusually large as though two sinuses had become fused. The mucosa over the sinus shows a characteristic reaction of menstruation with the separation of its superficial from its deeper layers by the extravasation of blood into the tissues of the mucosa (Fig. 7) and evidence that blood containing bits of the latter had escaped into the uterine cavity. There is just as strong evidence that some of this extravasated menstrual blood, carrying with it bits of the uterine mucosa, had escaped through the ruptured mucosal sinus into the lumen of the latter (see upper arrow). It is also possible that fragments of the uterine mucosa might be carried from the mucosal sinus into the receiving sinuses of the myometrium and thence into the deeper vessels of the uterine wall (see Figs. 23, 24 and 25). Only the beginning of the receiving sinuses of the myometrium, into which this mucosal sinus empties, appears in this section (see the two lower arrows).

FIG. 23*a*. Photomicrograph (× 25) showing a mucosal sinus undoubtedly emptying into a receiving sinus. It is a venous sinus and not a lymph vessel because the veins of the uterus had been injected with bismuth.

FIG. 23*b*. Photomicrograph (× 25) of the uterine mucosa and underlying muscularis from a section close to the one shown in Fig. 22. A vessel with the same structure, situation and general course as that shown in Fig. 23*a* is present and I therefore believe that it also is a venous sinus and not a lymph vessel. This sinus contains a small amount of blood and bits of endometrium (end) in both its mucosal and myometrial portions similar to those shown in the mucosal sinus of Fig. 22. I believe that it is possibly the receiving sinus into which the mucosal sinus, shown in Fig. 22, emptied. It is situated where the latter should be. (Unfortunately, serial sections had not been made. Many sections had been cut from the block and not all of them saved before the condition shown in Fig. 22 had been seen.)



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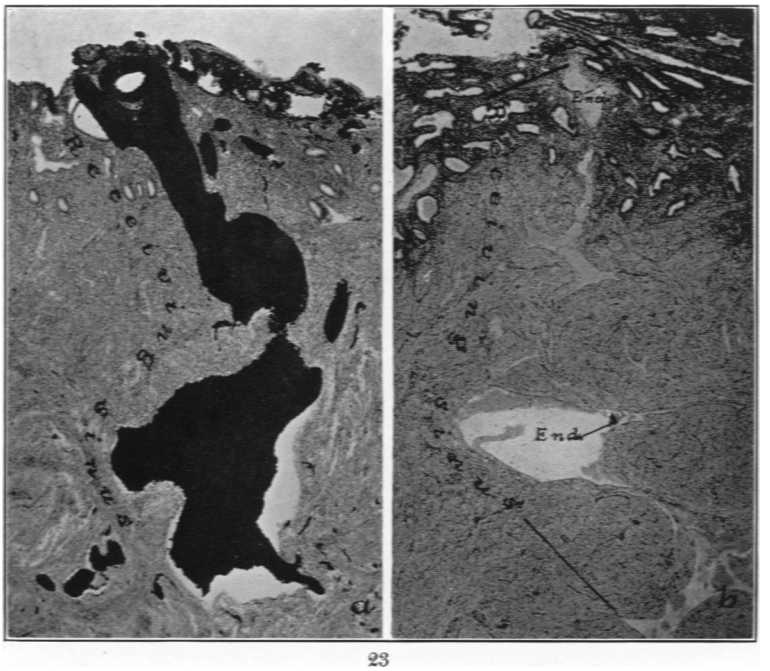

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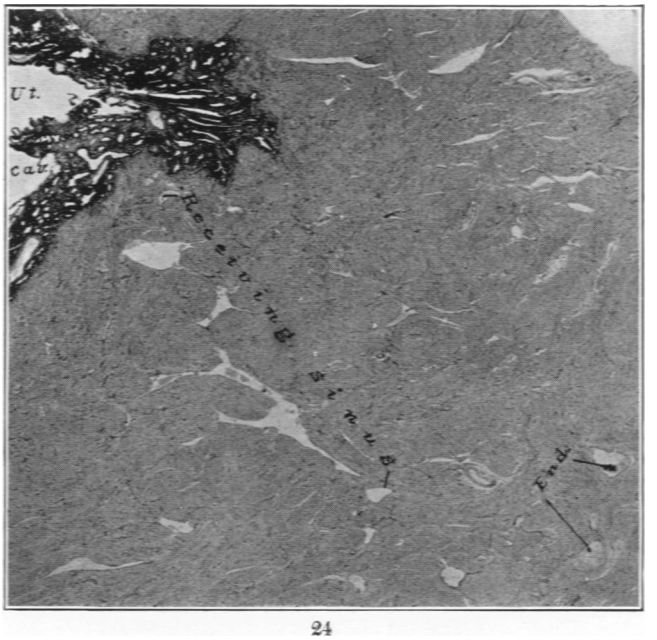
PLATE 27

FIG. 24. Photomicrograph (× 10) of a section from the same block of the uterine wall as those shown in Figs. 22 and 23. A receiving sinus is present radiating from the uterine mucosa (the same one shown in Fig. 23*b*). It contains a small amount of blood in places and also small bits of the uterine mucosa. Larger bits of the uterine mucosa are present in the vessels indicated by the pointer "End." (see Figs. 25 and 27). Serial sections were not made and therefore it cannot be proved that this receiving sinus emptied into the vessels containing the larger bits of the uterine mucosa but it probably did.

FIG. 25. Photomicrograph (× 60) of the two vessels containing bits of the uterine mucosa indicated by the pointer "End." of Fig. 24. Other sections demonstrate that these are but two sections of the same vessel. They contain bits of uterine mucosa surrounded by blood and the latter is adherent to the lining of the vessels, thus demonstrating that these fragments gained access to the lumen of the vessel before the tissues were fixed and are not artefacts as those shown in Figs. 20 and 21. The tissue in these vessels has the same histologic structure as that in the extravasated blood of the mucosa lining the uterine cavity, in the mucosal sinus and that in the receiving sinus. I believe that it reached its present situation by menstrual dissemination into the venous circulation of the uterus through the channels indicated in Figs. 22, 23 and 24.

FIG. 26. Photomicrograph (× 60) of a section of the uterine wall showing a mural thrombus attached to the lining of a vessel from the same block of the uterus as the section shown in Fig. 25. This vessel was situated a little deeper in the uterine wall than that shown in Fig. 25. For a higher magnification showing its histologic structure, see Fig. 27*b*.



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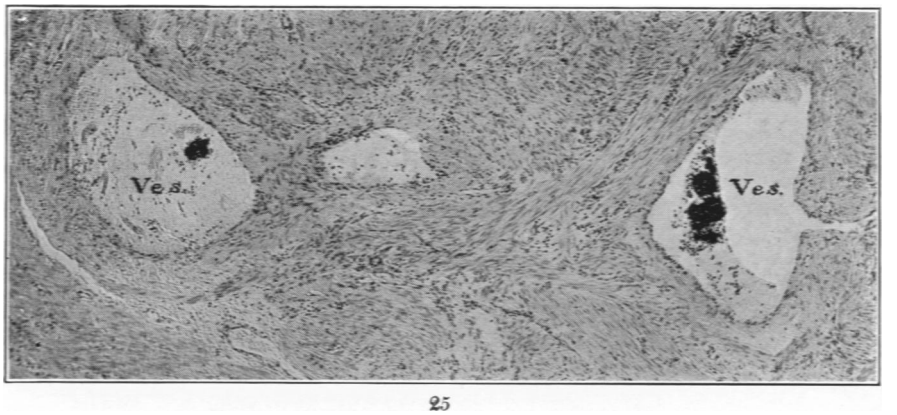

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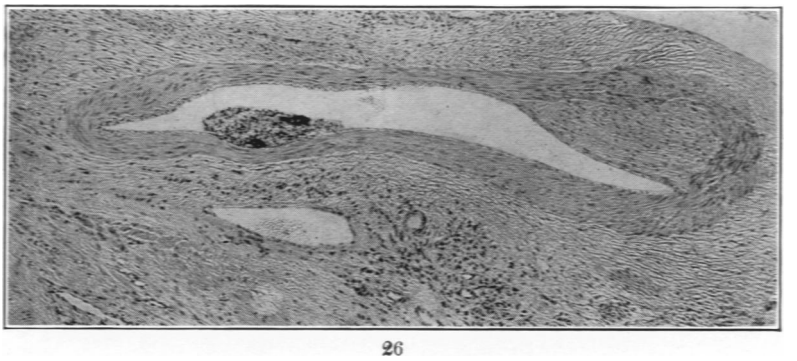

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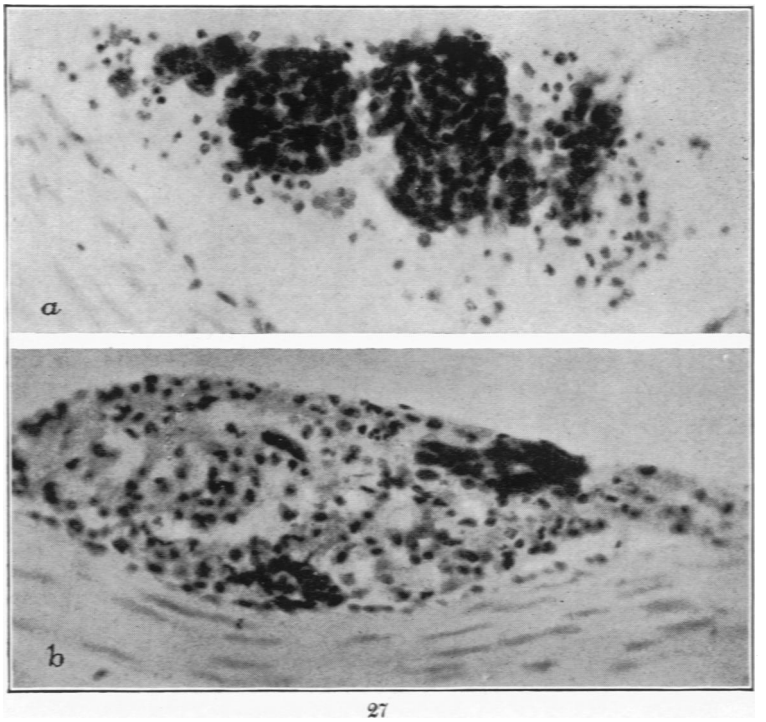
PLATE 28

FIG. *27a*. Photomicrograph (× 310) of the contents of the vessel containing the larger amount of endometrial tissue shown in Fig. 25. It consists of stroma and epithelium in a fair state of preservation and identical in their structure with that of similar bits of endometrial tissue in the extravasated blood of the uterine mucosa and in the mucosal sinus of the section shown in Fig. 22.

FIG. *27b*. Photomicrograph (× 310) of the mural thrombus shown in Fig. 26. The thrombus is attached to the endothelial lining of the vessel. It consists of fibrin, leucocytes, epithelium-like cells and two clumps of cells which might be interpreted as degenerating stromal cells. It would seem to represent a later stage of the condition shown in Fig. *27a* and might indicate that the "endometrial tissue" in the thrombus is either dead or at least in a poor state of preservation.

FIG. 28. Photomicrograph (× 310) of a portion of a peripheral vein in the fundus of the uterus showing blood and bits of "uterine mucosa" attached to the lining of the vessel (Case 2). The block from which the section was made was cut from the uterus after the latter had been hardened in formalin for a few days. The smaller fragment is adherent to the lining of the vessel while the larger is partially enveloped in blood and fixed to the wall of the vessel, thus demonstrating that they must have reached their present situation before the tissues of the specimen had become fixed. The last menstrual period occurred three weeks before the operation. More sections were made from the same block and a similar condition was found in another vein (see also Fig. 29).

FIG. 29. Photomicrograph (× 310) of a portion of an arcuate vein of the anterior uterine wall from the same uterus as the section shown in Fig. 28 but from a block taken from the uterus at a later date. Over a year after the operation many blocks were taken from the uterus and many sections were studied from each block, and in two vessels of the uterine wall embolic endometrial tissue was found, such as is shown here. The endometrial tissue is adherent to the lining of the vessel and the former stains poorly compared with the mucosa lining the uterine cavity (in the same section) thus suggesting that the former had undergone degenerative changes. The findings in these two cases demonstrate that bits of the uterine mucosa escape into the venous circulation of the uterus during menstruation and suggest that they may be retained in the sinuses of the uterine wall. They also suggest that this tissue may not always live.



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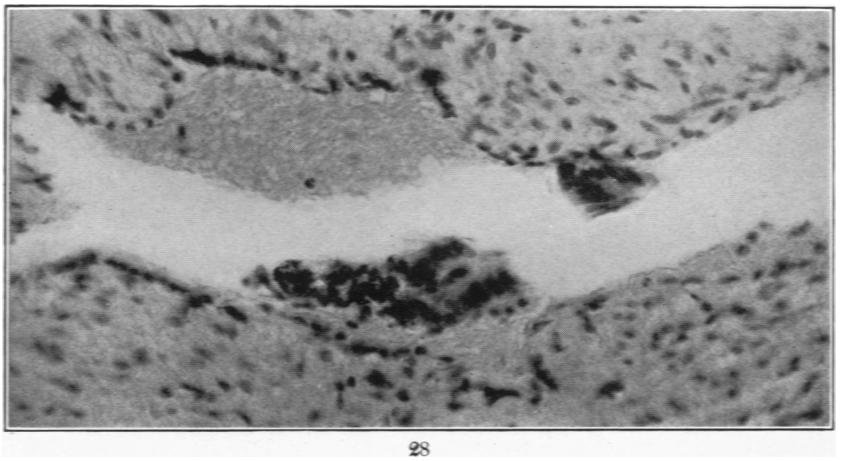

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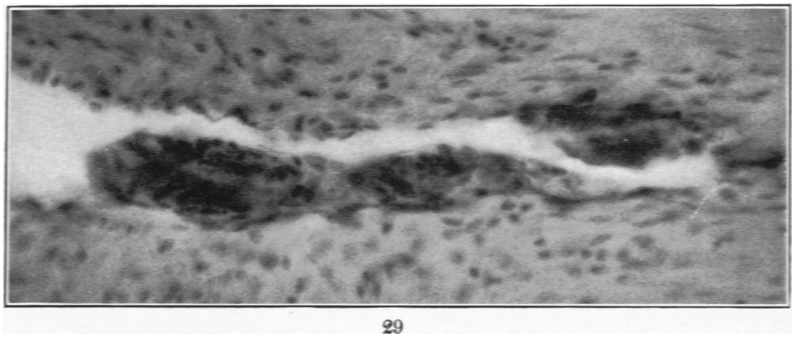

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PLATE 29

FIG. 30. Photomicrograph (× 20) of a section of the uterine wall, including its mucosa, demonstrating an embolus-like piece of the latter (M) in a receiving sinus (Case 3). Serial sections had been made of this portion of the block and it was shown that this receiving sinus extended into the mucosa and that the "embolus had lodged" at the site of a branching of the sinus. An endometriosis (End.) is present in this section of the uterine wall which, from an extra-endothelial position, bulged into a branch of the receiving sinus, as shown by sections of the block taken at another level and similar to the lesion shown in Fig. 14.

FIG. 31. Five photomicrographs (× 60) of sections showing the appearance of the endometrial tissue in the receiving sinus of Fig. 30, at different levels of the series. *a* shows a bit of stroma apparently adherent to the lining of the sinus but really not attached. *b* (from the same section shown in Fig. 30) demonstrates epithelium arranged in the form of a gland and surrounded by stroma. This tissue apparently lies free in the lumen of the sinus at this level as does also the tissue shown in *c*. *d* demonstrates that the bit is really a polyp, attached by a slender pedicle to the wall of the sinus (for a higher magnification of this polyp see Fig. 33). *e* shows the last appearance of the epithelium in the polyp with a fragment of stroma to the left of it. The series of sections from which these were chosen demonstrated that an endometrial polyp was present in this sinus attached by a pedicle to the wall of the latter and apparently surrounded by endothelium just as similar polyps arise from the invasion of endometrial tissue into a vessel pushing the endothelium ahead of it (see Figs. 14 to 18 inclusive, from the same case) but differing from the latter in that it was conclusively shown that the gland lay entirely within the sinus and was not a cross-section of a tubule continuous with a similar structure outside of the vessel.

FIG. 32. Four photomicrographs (× 60) of sections showing embolic "uterine" epithelium attached by fibrin to the wall of a receiving sinus. From the same block of the uterine wall as the sections shown in the preceding illustrations but at a different level and in another portion of the block. Serial sections demonstrated that the epithelium, arranged in the form of a gland, lay entirely within the sinus, was not covered by endothelium and was not continuous with any endometrial tissue outside of the sinus. It is attached to the wall of the sinus by fibrin, thus demonstrating that it reached its present situation before the tissues had been fixed, either from the trauma of the operation, the incision of the uterus immediately after the operation or the menstrual dissemination of this tissue into the sinus (patient flowing at the time of the operation). For a higher magnification of the lesion in *c* see Fig. 34.

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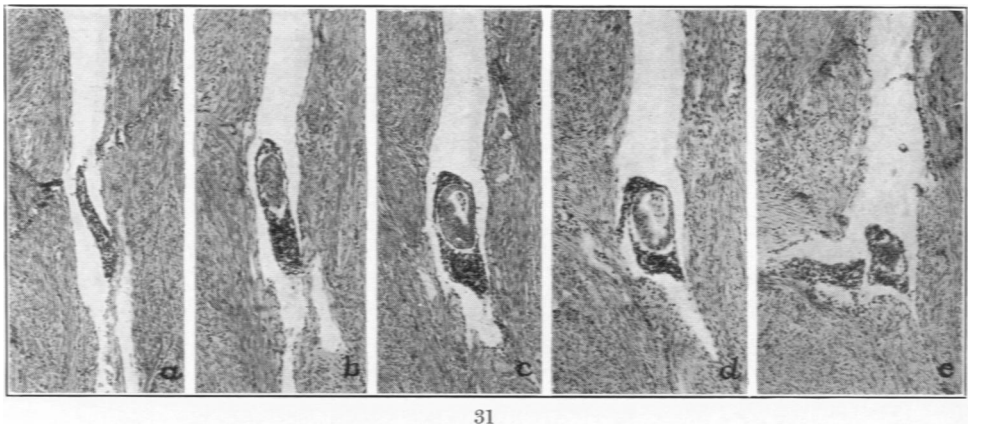

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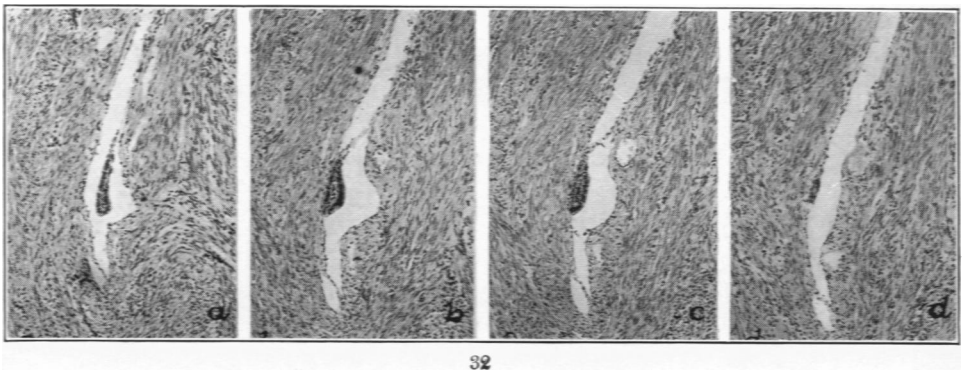

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PLATE 30

FIG. 33. Photomicrograph (× 310) of the endometrial polyp shown in *d* of Fig. 31. It consists of an epithelial gland surrounded by endometrial stroma and the latter apparently covered by endothelium; it is extra- or retro-endothelial and is attached to the wall of the sinus by a slender pedicle. This endometrial polyp must have arisen either from a metaplasia of the endothelial lining of the sinus, an implantation of a bit of the uterine mucosa escaping into the sinus during menstruation (Fig. 31), an implantation from the menstrual reaction of the heterotopic endometrial tissue bulging into a branch of the sinus (see Fig. 31) but separated from the lumen of the sinus by its endothelial lining, or if it previously had been continuous with the latter this connection in some way must have been severed. For a possible explanation of its origin see Fig. 34.

FIG. 34. Photomicrograph (× 310) of the "uterine" epithelium attached to the wall of the sinus by fibrin (Fig. 32*c*). The epithelium is arranged in the form of a gland and is entirely intravascular. Its possible origin was discussed in the legend of Fig. 32. If it is a menstrual embolus, as well it might be, the origin of the polyp shown in Fig. 33 can readily be explained. Should the endothelium of the sinus cover such an implant and the endometrial tissue live, it might readily develop into a polyp similar to that shown in Fig. 33 or a lesion similar to that shown in Fig. 35.

FIG. 35. Photomicrograph (× 310) of a portion of a sinus, a branch of the sinus shown in Figs. 30 and 31, with extra-endothelial endometrial tissue bulging into its lumen. Serial sections demonstrated that this endometrial tubule was not continuous with the gland in the polyp shown in Fig. 33. The series beyond this portion of the block was incomplete and the relation of this endometrial tissue to that outside of the sinus was not determined. I believe that it might have been continuous with the latter. If true, the latter might have arisen from this and not the reverse. The conditions shown in Figs. 33 and 34 suggest that this endometrial tissue might have developed from the implantation of embolic endometrial tissue with a subsequent growth of the endothelium of the sinus over it.

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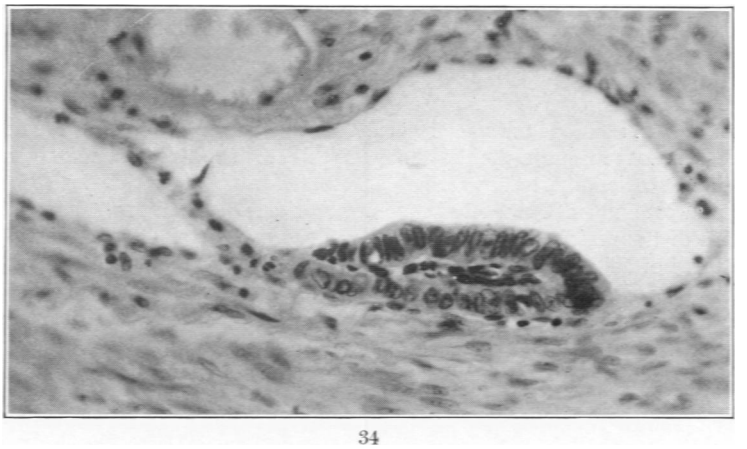

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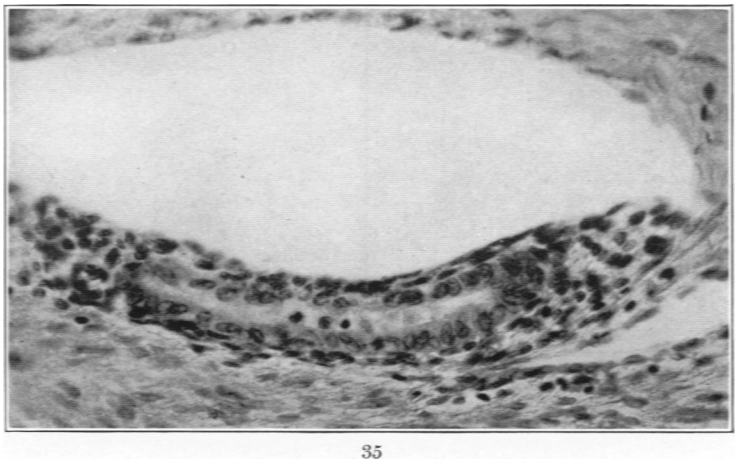

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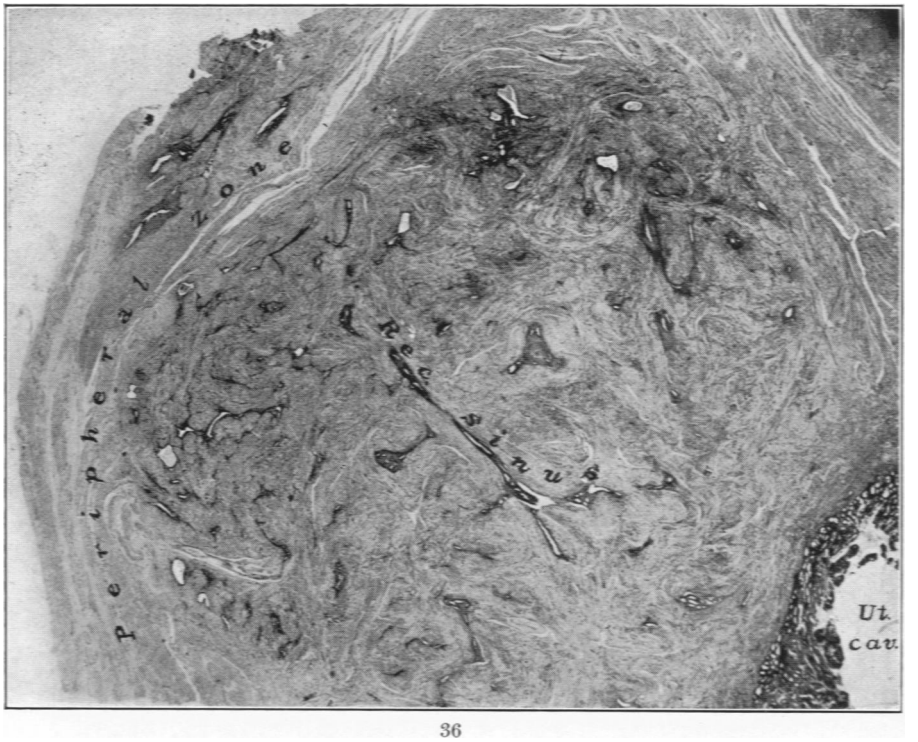
PLATE 31

FIG. 36. Photomicrograph (× 5) of a section of the left half of the posterior uterine wall (Case 4). An endometriosis is present, most marked in the radial zone. The distribution of the endometrial tissue in that zone is similar to the distribution of the bismuth in corresponding sections of uteri in which the veins have been injected. In this section many of the spaces occupied by the veins and venous sinuses of the uterine wall are filled with endometrial tissue (Fig. 38). An apparent receiving sinus (Fig. 39) is well outlined by this tissue. The entire uterus was cut into blocks and many sections were studied from each block and in only a small area was an invasion of the uterine wall by its mucosa found. I believe that the endometriosis of the radial zone shown in this photomicrograph possibly arose from this invasion. The endometriosis of the peripheral zone was more likely of embolic or metastatic origin. While the patient was menstruating at the time of the operation, only a very few of the areas of ectopic endometrial tissue showed a reaction to menstruation (Fig. 40).

FIG. 37. Photomicrograph (× 5) of a section of the right half of the posterior uterine wall at about the same level as that shown in Fig. 36. An endometriosis is not present in the radial zone of this section. An embolic implantation of endometrial tissue (End.) is situated in the arcuate veins (Figs. 49 and 50) and small emboli of endometrial tissue (E,E) are present in the veins of the peripheral zone (Fig. 51). There were two very interesting features of this uterus; one was the presence of an endometriosis of the direct type in the left half of the posterior uterine wall with only a very few evident embolic lesions and those in the peripheral zone; the other was multiple embolic lesions in the right half of the posterior uterine wall, most numerous in the peripheral zone with only a slight invasion of that half of the posterior uterine wall by the endometrial tissue from the opposite side.



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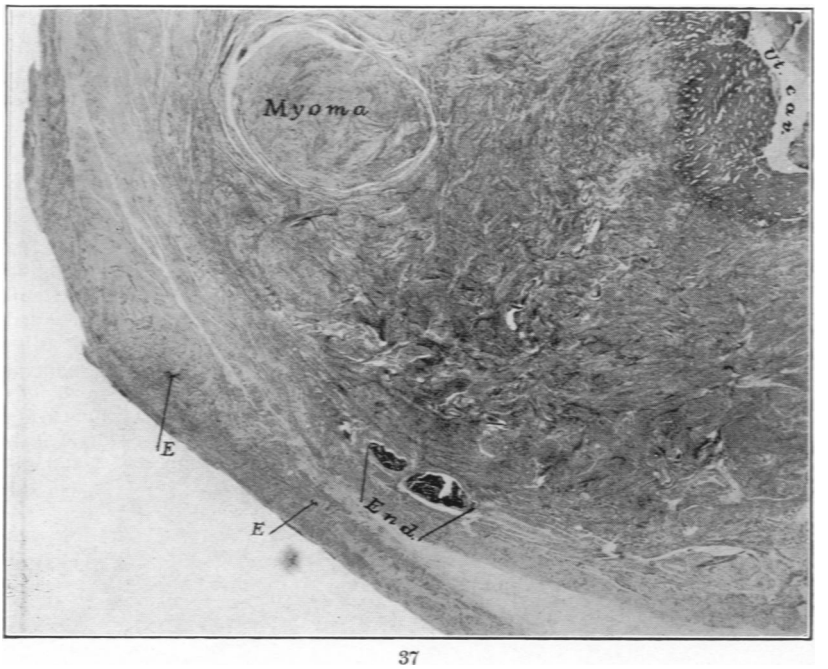

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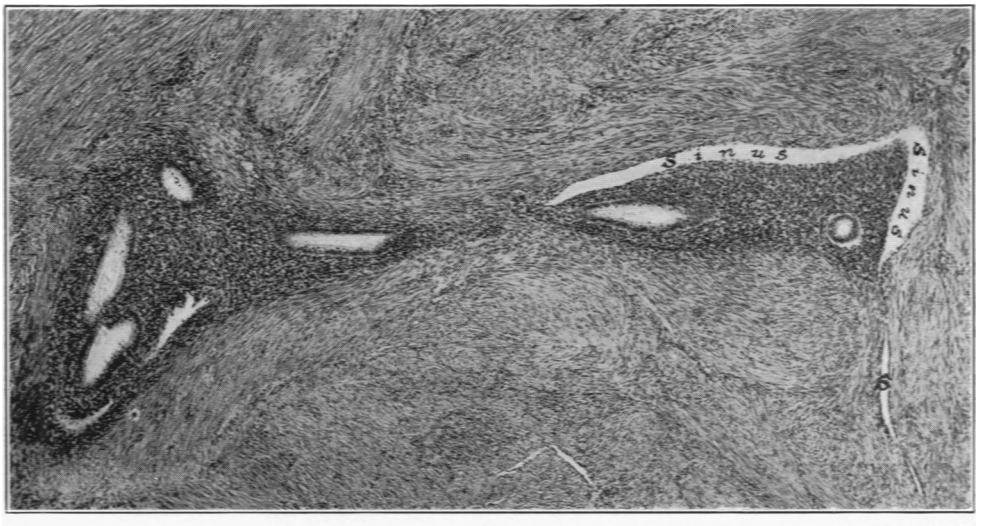
PLATE 32

FIG. 38. Photomicrograph (× 60) of a portion of the section shown in Fig. 36 illustrating a frequent type of lesion found in a direct or primary endometriosis. No trace of a vessel or sinus is evident in or about the endometrial area to the left. I believe that it fills the space originally occupied by a sinus and has either obliterated the lumen of the latter or pushed it to one side. The endometrial area to the right, a continuation of the former, projects into the lumen of a sinus like a sessile polyp but the surface of the latter is covered by endothelium. The endometrial tissue is invading the space occupied by the sinus in a retro-endothelial course, as has been so well described by Robert Meyer. I believe that this vessel is probably a venous sinus and not a lymphatic. It is conceivable that, should this endometrial tissue react to menstruation, blood containing bits of endometrial tissue would escape into the lumina of its tubules (see Fig. 40) and at times might rupture the overlying endothelium and escape into the lumen of the sinus.

FIG. 39. Photomicrograph (× 25) of a portion of the "receiving sinus" shown in Fig. 36. The space occupied by the sinus is partially filled by endometrial tissue. The endometrial tissue has apparently invaded this sinus in a retro-endothelial course distorting the lumen (L.) of the latter as shown in Fig. 38 and in the manner of a direct or primary endometriosis. A direct invasion of this portion of the uterine wall by its mucosa was found and this is possibly a continuation of it. On the other hand, its histologic structure suggests a "canalized" endometrial thrombus which might have arisen from the implantation and growth of an embolus of endometrial tissue on the lining of the sinus with subsequent covering by endothelium. As will be shown, it is possible for the endothelium of a vessel or sinus to grow over endometrial tissue implanted in that vessel and give rise to lesions somewhat similar to those shown in this and the preceding illustration (see Figs. 41, 42 and 50).

FIG. 40. Photomicrograph (× 60) of a section of a menstruating area in the endometriosis shown in Fig. 36. An endometrial cavity (dilated tubule) is filled with blood and bits of endometrial tissue. This blood might extend through the lumen of the tubule to other parts of the uterine wall invaded by this tissue. The endothelial lining of a venous sinus in this area or adjacent to it might be ruptured by the menstrual reaction, and menstrual blood carrying with it bits of the uterine mucosa, might escape into the venous circulation of the uterus. I have not been able definitely to demonstrate this in the menstrual reaction of endometrial tissue of a direct endometriosis but am confident that it does take place. For anatomic and physiologic reasons it should occur and I have observed it in an endometriosis of the posterior vaginal wall (Figs. 60 and 61).



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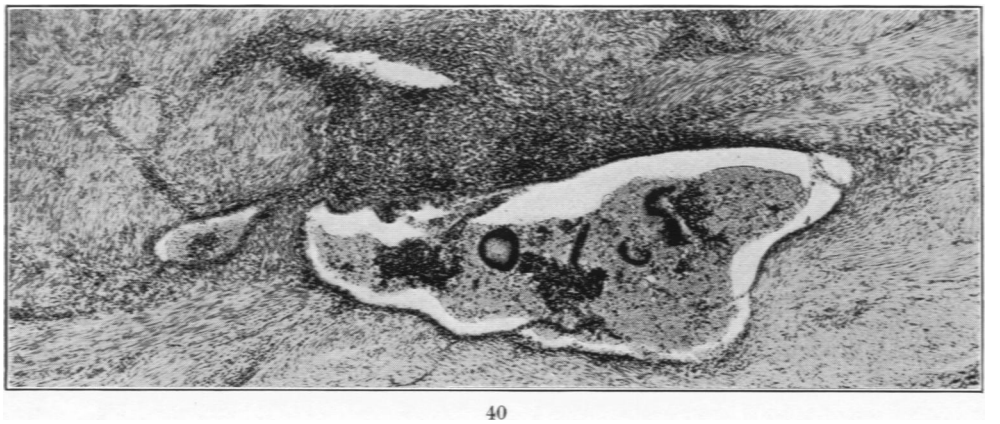

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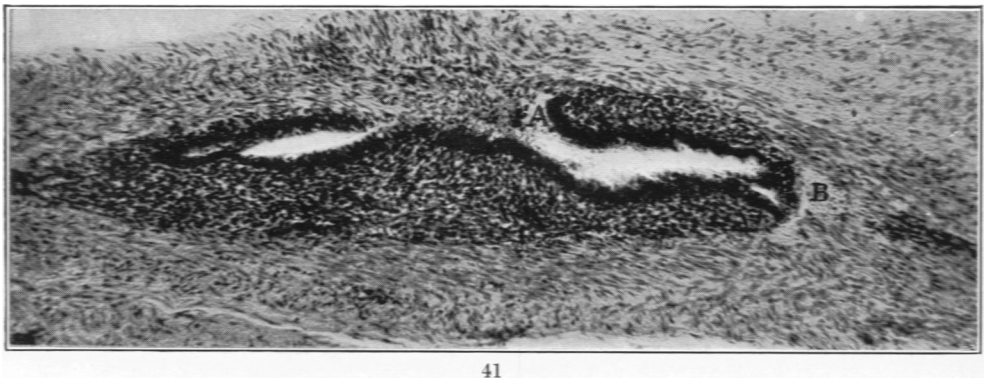
PLATE 33

FIG. 41. Photomicrograph (× 130) of an oblique section of a sinus almost completely filled with endometrial tissue (from the peripheral zone of the left half of the posterior uterine wall near the midline). Sufficiently complete serial sections were made to demonstrate that this tissue was not continuous with that in the radial zone or any outside of the sinus, but arose either from an implantation of a bit of endometrial tissue on the lining of this sinus or else from a metaplasia of its endothelial lining. I believe the former (see Figs. 42 and 43). In this section the implant is not attached to the wall of the sinus at A and B. The endometrial cavity, lined by epithelium, communicates with the lumen of the sinus at A. Should menstrual blood escape into this endometrial cavity, as shown in Fig. 40, it might carry with it bits of endometrial tissue into the lumen of the sinus and thence into the venous circulation of the uterus. At B the implant bulges into the lumen of the sinus but its surface is covered by endothelium, growing over it from that lining the sinus. This implantation lesion differs from that arising from the invasion of a sinus by endometrial tissue from without in that it is primarily intravascular while the latter is extravascular (retro-endothelial). Should complete endotheliazation of an implant occur, it might be histologically indistinguishable from that of a direct invasion and in its subsequent growth it might invade the lumen of the sinus as a retro-endothelial course and thus give rise to lesions similar to those shown in Figs. 36, 38 and 39. I have not been able to prove that this occurs.

FIG. 42. Photomicrograph (× 130) of the same sinus shown in Fig. 41 but at one end of the implant. At the right, the endometrial tissue is grafted on the wall of the sinus. To the left it is attached to the wall of the sinus by fibrin and endothelium apparently has begun to cover it. While the lesion shown here probably is an extension of the endometrial tissue shown in Fig. 41 it could well represent a stage in the implantation of embolic endometrial tissue lodging in a sinus (see Fig. 43).

FIG. 43. Photomicrograph (× 130) of the same sinus shown in Figs. 41 and 42 but beyond the implant. The sinus is partially filled with blood containing free bits of endometrial tissue possibly cast off by menstruation from the implant or from endometrial tissue elsewhere in the uterus as indicated below. Should this tissue become attached to the wall of this or another sinus and live, the lesions shown in Figs. 41 and 42 might arise. I believe that the lesion shown in Fig. 41 arose in this manner — from embolic endometrial tissue either cast off from another implant, from the menstrual reaction of a direct endometriosis with rupture into a vein, or from the menstruating uterine mucosa disseminating bits of endometrial tissue into the venous circulation of the uterus.



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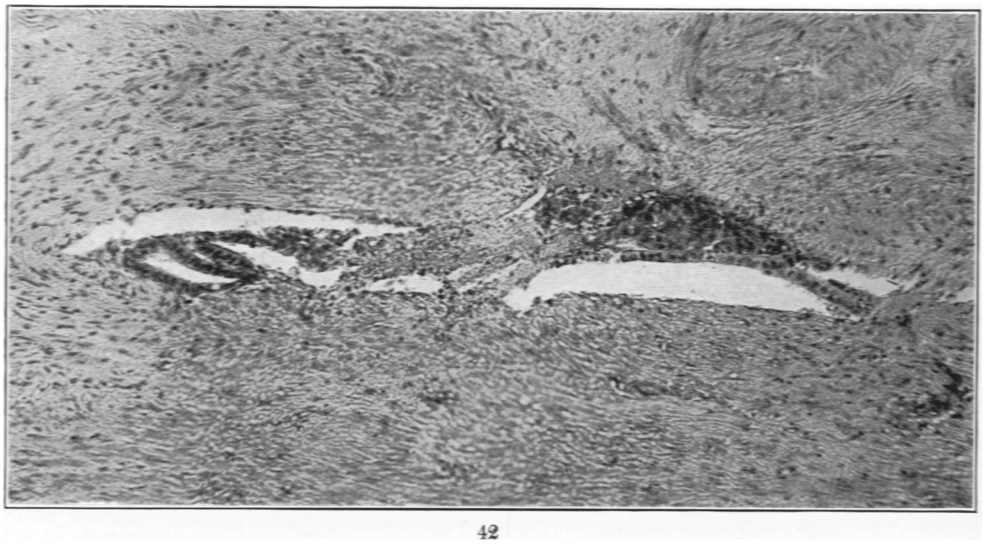

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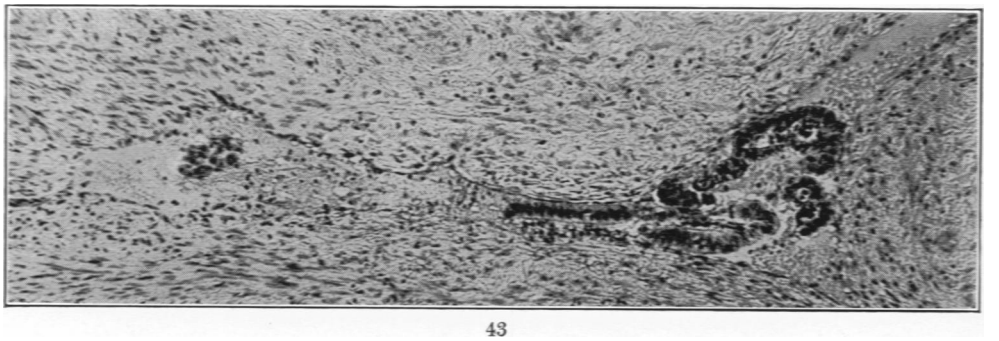

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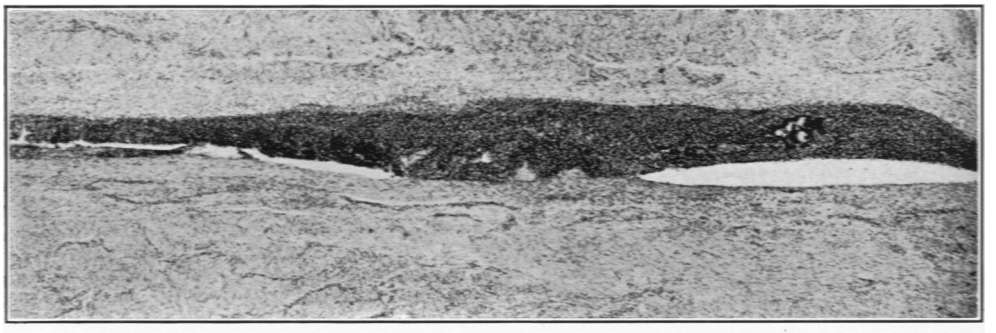
PLATE 34

FIG. 44. Photomicrograph (× 25) of an arcuate vein in the lower portion of of the posterior uterine wall. The lumen of the vessel is almost completely filled with endometrial tissue. It resembles the lesion of a direct endometriosis but is also similar to that shown in Fig. 41. This was the first section obtained after trimming the block and therefore it was impossible to ascertain whether or not it is of embolic origin. My reaction is that it is of embolic origin. This lesion was followed through the block until it disappeared (see Figs. 45 and 46).

FIG. 45. Photomicrograph (× 25) of the same vein shown in Fig. 44 but deeper in the block. It differs from the latter in that the lumen of the endometrial tubule (cavity) communicates with that of the vein at A and also at B. The latter might be an artefact (torn in cutting) but not the former (see Fig. 47).

FIG. 46. Photomicrograph (× 25) of the vein or branches of the same shown in Fig. 44. A little beyond this level the lesion disappeared. The lesions are similar to those shown in Fig. 38 and circumstantial evidence indicates that the latter might have arisen from the direct invasion of the uterine wall by its mucosa.

FIG. 47. Photomicrograph (× 130) of the portion of the vein indicated by A of Fig. 45. The endothelial lining of the vessel is well shown in the upper portion of the right half of the photomicrograph. The lumen contains blood and is loosely filled with stroma. The endometrial cavity to the left empties into the lumen of the vein. It is not an artefact. It represents either the incomplete grafting of an endometrial implant as shown in Fig. 41 or else the endothelial covering of the endometrial tissue of a direct endometriosis has been destroyed by menstruation. My present reaction is that it is the former (compare with Fig. 41 which we know is of embolic origin).



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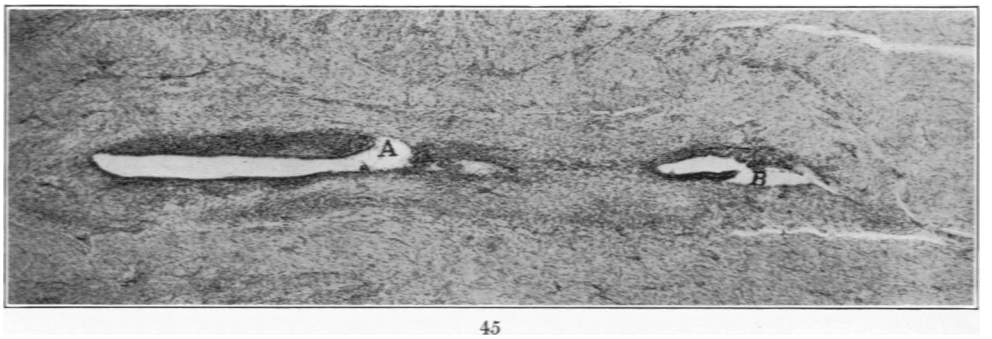

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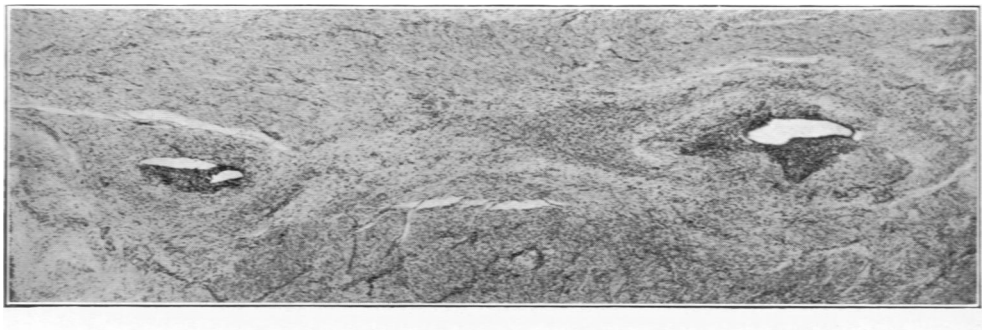

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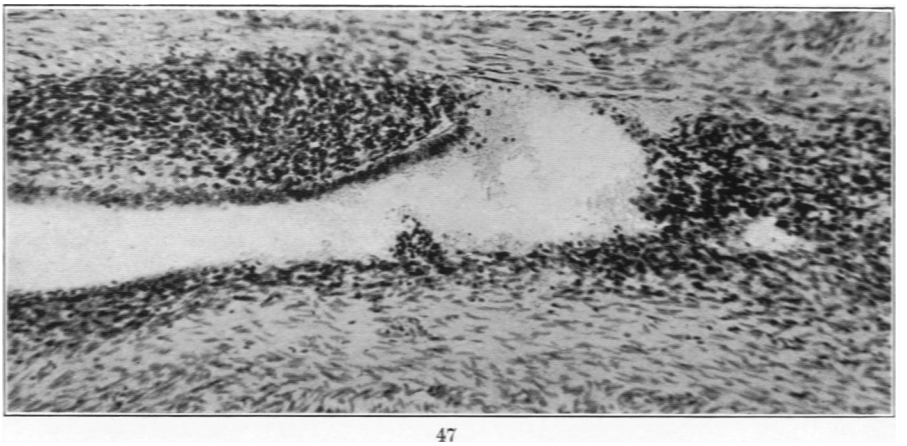

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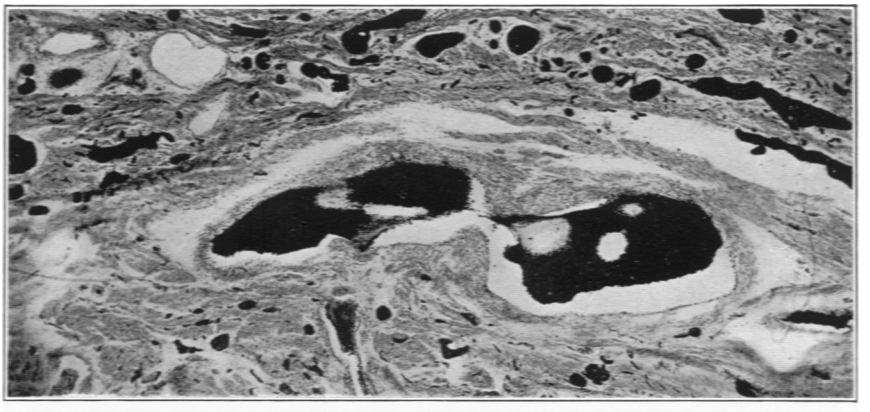
FIG. 48. Photomicrograph (× 25) of a section of the uterine wall showing an arcuate vein cut obliquely; veins injected with bismuth. The blood from the peripheral and radial zones of the uterus empties into the arcuate veins and is conveyed by these to the venous circulation outside of the uterus. Bits of endometrial tissue carried by menstrual blood into the ruptured venous sinuses of the uterine mucosa (Figs. 22 and 23) would reach these veins through the receiving sinuses (Figs. 9 and 10). These bits might become implanted in these veins (Fig. 49) or under the varying changes in the pressure of the venous circulation of the uterus they might be carried into vessels of the peripheral zone (Figs. 11, 51 and 65) or even escape into the venous circulation outside of the uterus.

FIG. 49. Photomicrograph (× 25) of a section of the arcuate vein shown in "End." of Fig. 37. It is almost an exact duplication of the vein shown in Fig. 48 except that the injection mass is replaced by endometrial tissue. Sufficiently complete serial sections were made of this block to demonstrate that the endometrial tissue in the vein did not arise from the invasion of the vessel by endometrial tissue outside of it. The endometrial tissue in this section is entirely intravascular and must have arisen either from a "metaplasia" of the endothelium of the vessel or else through the implantation and growth of an endometrial embolus similar to those found floating about in lumina of other vessels (see Figs. 43, 53 and 65). The endometrial tissue of this implant has the same structure as that of the mucosa lining the uterine cavity (Fig. 55) and that found in the endometriosis of the opposite side of the posterior uterine wall shown in Figs. 36, 38 and 39.

FIG. 50. Photomicrograph (× 25) of another section of the arcuate vein shown in Fig. 49. The lesion differs from the preceding one in a very important feature. The endometrial tissue in the former is entirely intravascular while that in this section is partially retro-endothelial due to the growth of the endothelium of the vessel over the end of the endometrial tissue projecting into the lumen of the vein (to the left) just as endothelium covers a mural thrombus. Should the endothelium grow more rapidly than the endometrial tissue, it might cover the entire unattached portion of the endometrial implant. Should bits of endometrial tissue be cast off by the menstrual reaction of such an implant they would escape into the venous circulation of the uterus. Some of the endometrial emboli in this specimen might have had such an origin (Fig. 65).

FIG. 51. Photomicrograph (× 25) of a section of the peripheral zone of the uterine wall from the same block shown in Fig. 37 and very near the latter. Bits of endometrial tissue (End.) are present in the veins of this section, some lying free in the lumen of the vessel and others attached to its wall. (For a higher magnification of similar lesions in another section of the peripheral zone see Fig. 65.) These bits of endometrial tissue must have arisen from the dissemination of similar tissue into veins of the peripheral zone from the menstrual reaction of an endometrial implant such as that shown in Figs. 41 and 49, or from the menstrual reaction of the uterine mucosa discharging menstrual blood into a ruptured mucosal sinus as has been demonstrated, or from a similar reaction of the endometrial tissue of a direct endometriosis which must occur but which I have not been able definitely to prove.



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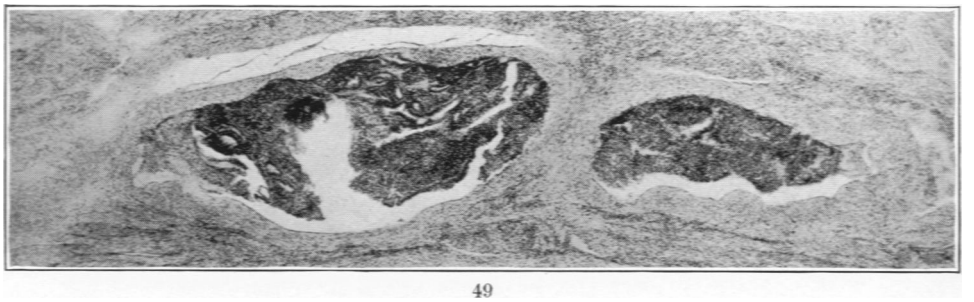

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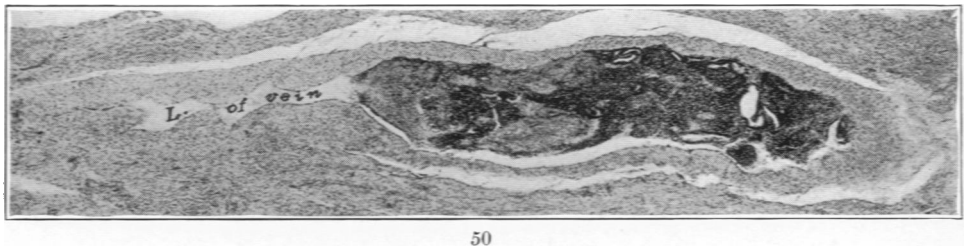

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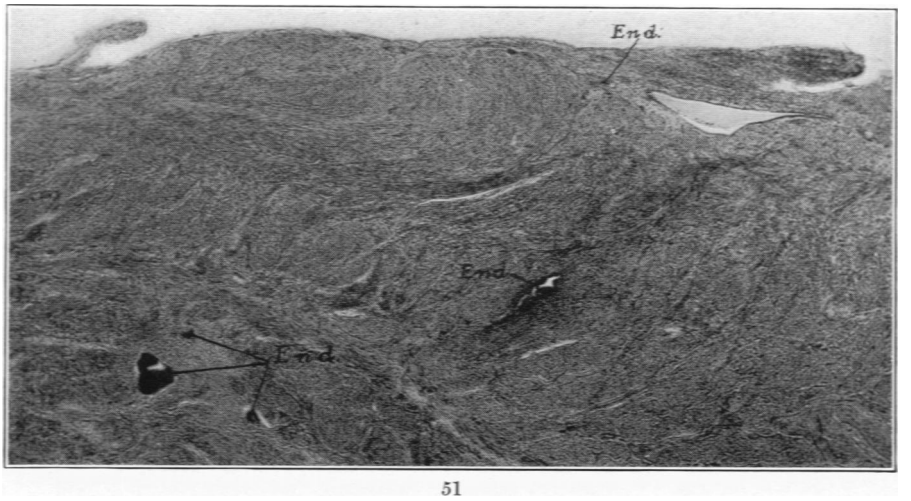

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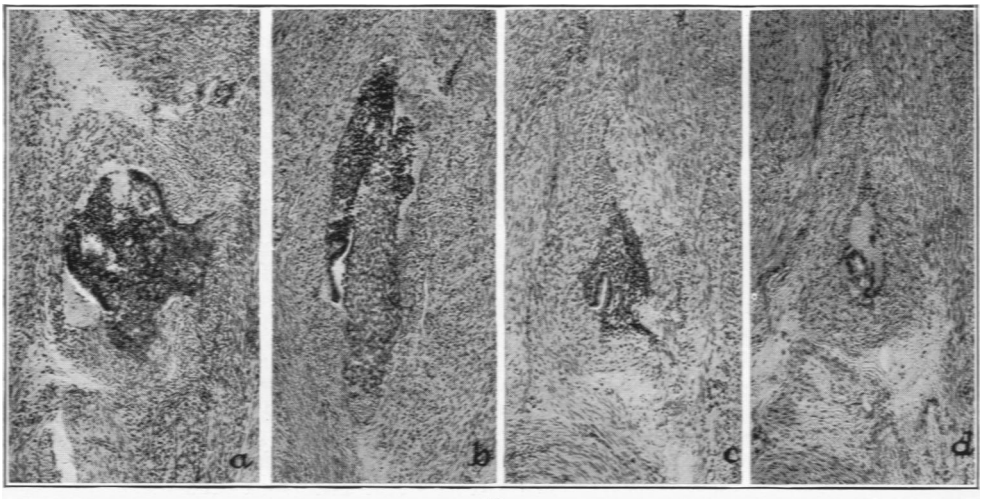
PLATE 36

FIG. 52. Four photomicrographs (× 60) from a series of sections showing the appearance, at different levels, of an embolic implantation of endometrial tissue in a vein or sinus of the peripheral zone of the right half of the posterior uterine wall. *a* shows the condition found near one end of the "endometrial plug" and *d* that found near the other end. In *a* and *d* there is no evidence of endotheliazation while in *b* and *c* the implant is apparently partially covered by endothelium. Many lesions similar to this one were found in the peripheral zone of the right half of the posterior uterine wall.

FIG. 53. Three photomicrographs of sections of veins in the right half of the posterior uterine wall. *a* (× 60) shows a bit of endometrial tissue surrounded by blood in the lumen of a large vein near the lateral surface of the uterus, very close to the uterine plexus and therefore almost in the venous circulation outside of the uterus by which it could easily be carried to the lungs. *b* (× 130) shows a bit of uterine epithelium attached to or resting on the lining of a sinus of the radial zone. It is situated between the mucosa lining the uterine cavity and the arcuate veins and is in a channel by which endometrial tissue escaping from the uterine mucosa would reach these veins. *c* (× 60) shows an embolic endometrial implant in a sinus of the peripheral zone with no evidence of endotheliazation.

FIG. 54. Photomicrograph (× 25) of an embolic growth of endometrial tissue in a receiving sinus of the right half of the posterior uterine wall. It more than suggests that this endometrial tissue primarily escaped into this sinus from a sinus of the uterine mucosa and that similar bits might have reached the arcuate veins into which the receiving sinuses empty and from the arcuate veins escaped into the peripheral veins of the uterine wall. I believe that the embolic lesions of endometrial tissue in the veins and sinuses of the right half of the posterior uterine wall primarily arose from the menstrual dissemination of bits of the uterine mucosa into the venous circulation of the uterus rather than from a similar reaction of the endometrial tissue of a possible direct endometriosis.



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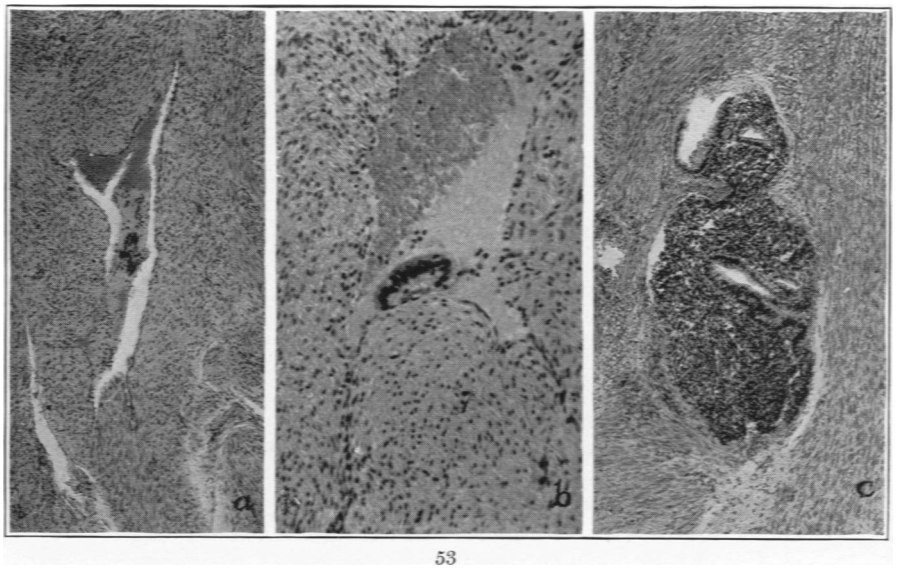

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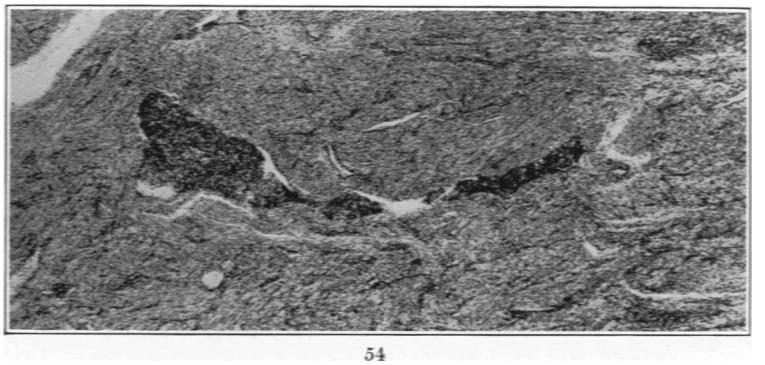

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PLATE 37

FIG. 55. Photomicrograph (× 25) of the menstruating mucosa lining the uterine cavity (Case 4). A mucosal sinus is present containing blood and a bit of endometrial tissue (End.). It might be argued that the latter is an artefact in this instance and gained access to the lumen of the sinus from the trauma of the operation or in cutting the blocks from the hardened specimen. Should such a bit escape into the lumen of a mucosal sinus during menstruation, as they do, we might expect to find similar fragments in the sinuses of the uterine wall including the receiving sinuses and also in the arcuate veins and even those of the peripheral zone. As has been shown, not only were these found but also the actual implantation and growth of this tissue in these vessels, thus demonstrating that bits of endometrial tissue disseminated by menstruation are sometimes alive and capable of becoming implanted on the endothelial lining of the veins and venous sinuses of the uterine wall.

FIG. 56. Photomicrograph (× 10) of a section of a portion of the anterior uterine wall near one of the cornua with the anterior layer of the broad ligament fused to it by the endometriosis in this situation. The anterior cul-de-sac was partially obliterated by a peritoneal endometriosis fusing the anterior surface of the uterus with the anterior layer of the broad ligament and the peritoneum covering the bladder. The lesion was most marked about the uterine cornua. The lumen of the cul-de-sac is patent at both ends of the section ($a - a$ and $b - b$) but is occluded in the center. It would seem that the lesion started at X possibly on or near the peritoneal surface of the uterus and radiated in all directions invading the uterine wall and the anterior layer of the broad ligament to about the same depth. The entire uterus was cut into blocks and many sections were studied from each block. No endometrial tissue was found in the anterior uterine wall except similar to that indicated in this section. Definite embolic lesions, like those in the right half of the posterior uterine wall, were not found in any portion of the lesion. The endometrial lesions in this section and in all others from this portion of the specimen showed an endometriosis of the invasive type apparently spreading from or near the peritoneal surface of the uterus. In a few areas a possible communication of the lumen of an endometrial tubule with that of a vessel was suggested, thus indicating a possible metastatic origin. Three theories may be considered for the origin of the endometrial tissue in this situation. 1. From the stimulation of potential endometrial tissue in the serosa. 2. From the implantation of endometrial tissue on the peritoneum from menstrual blood escaping into the cul-de-sac. Both tubes were patent and endometrial tissue was not found in the ovaries. 3. From endometrial emboli lodging in subperitoneal vessels of the peripheral zone of the anterior uterine wall. I have been unable to determine its origin but believe that primarily it must have been either an implantation or an embolus.

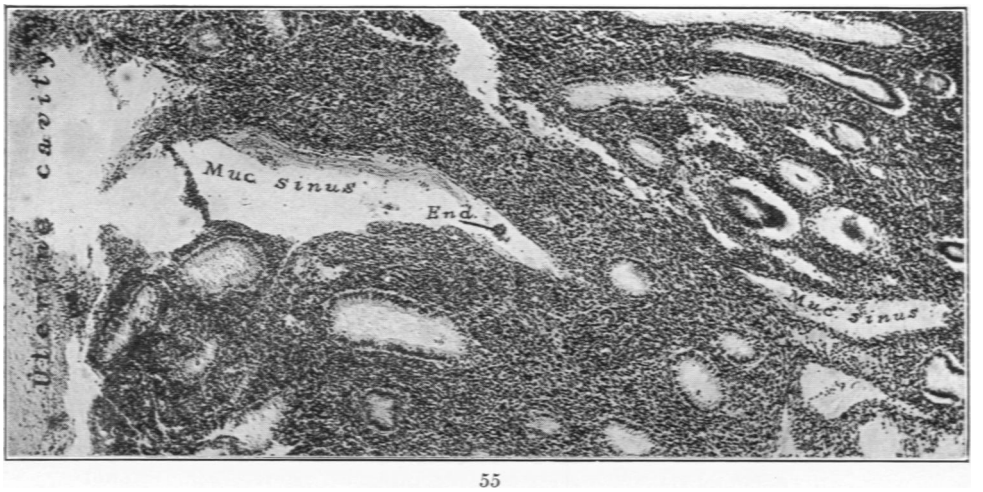

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PLATE 38

FIG. 57. Photomicrograph (× 10) of a longitudinal section of a portion of the posterior vaginal wall near the cervix (Case 4). An endometriosis is present showing a variety of endometrial lesions including cavities filled with blood (patient menstruating at the time of the operation). The endometrial tissue in this situation may have been primarily derived from a direct extension downward from that in the cul-de-sac or emboli in the venous circulation of the uterus may have been carried to the vaginal wall through the vaginal veins. I believe that the former is the more likely source.

FIG. 58. Photomicrograph (× 25) of a portion of the section shown in Fig. 57. A cavity is present partially lined by epithelium and filled with blood containing bits of endometrial tissue cast off by the menstrual reaction. Bits of endometrial tissue, End., identical with those in the cavity are present in small veins to the right of this cavity. Some of these fragments lie free in the blood of these veins and others are attached to or implanted on the walls of the vessels (Figs. 59 and 65). What is the origin of the endometrial emboli in these vessels? Are they metastatic from the uterus or were they disseminated from the ectopic endometrial cavities in the vaginal wall? I believe the latter (see Figs. 60 and 61).

FIG. 59. Two photomicrographs (× 130) of portions of the section shown in the preceding illustration. *a* is a longitudinal section of a vein with a small bit of endometrial tissue lying free in its blood, *b* a cross-section of a vein with a strip of epithelium "buckled" in its lumen and *c* a cross-section of a vein distended by endometrial tissue growing in the vessel. For a photomicrograph of another vein containing endometrial tissue see Fig. 66.

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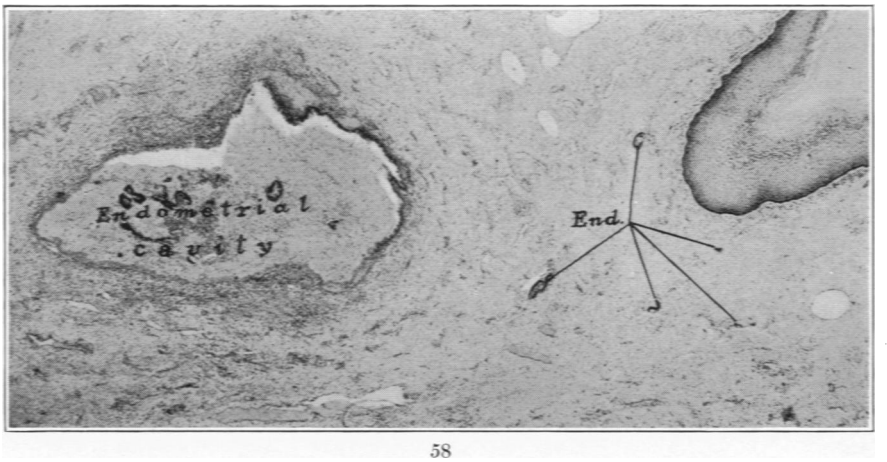

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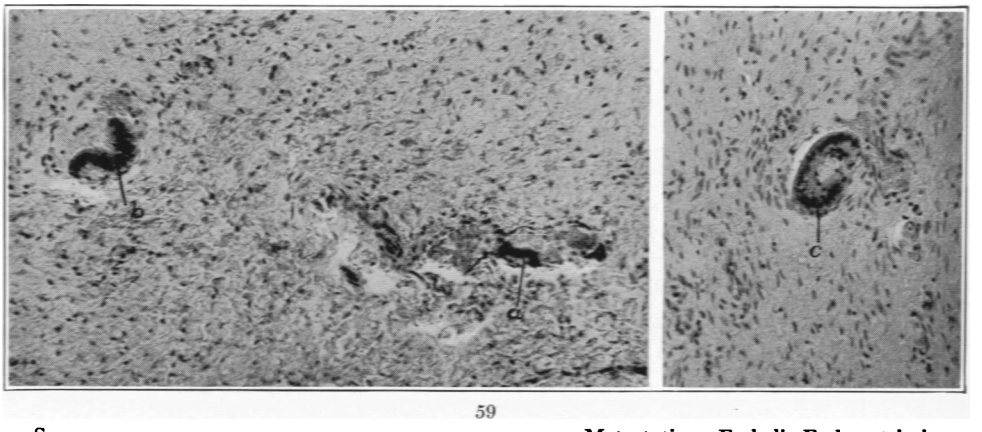

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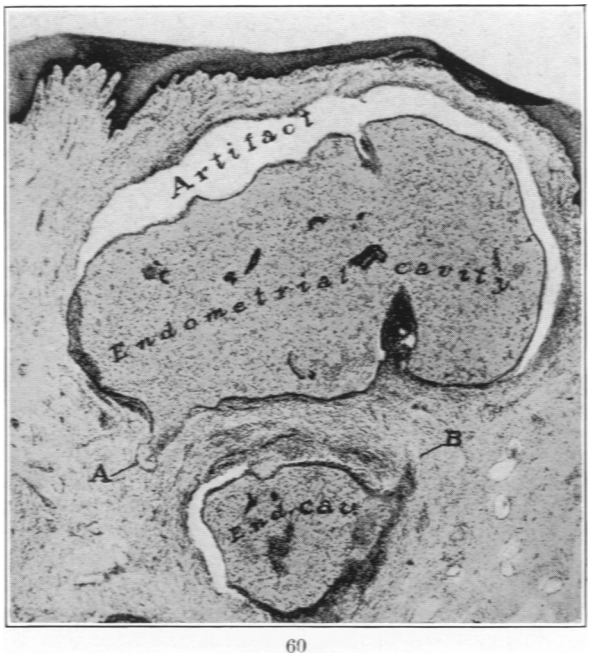
PLATE 39

FIG. 60. Photomicrograph (× 25) of a section from the same block as the preceding. Two endometrial cavities are present, the larger just beneath the vaginal mucosa. Both of these cavities are filled with blood (menstrual) containing cast-off bits of endometrial tissue. The smaller cavity has ruptured into a vein at B and some of its contents are escaping into the lumen of the vein. The larger cavity has also ruptured into a vein at A and some of its contents are likewise escaping into the lumen of this vein (see Fig. 61).

FIG. 61. Photomicrograph (× 310) of a portion of the section shown in A of Fig. 60. The endometrial cavity, above, has ruptured through the endothelial lining of the vein and some of the contents of the former have escaped into the lumen of the vein. I believe that the endometrial emboli in the veins of the vaginal wall already shown (Figs. 58 and 59) had a similar origin. As some of these emboli have become implanted on the lining of these vessels (see Figs. 59 and 66) it is again evident that bits of endometrial tissue, cast off by menstruation, are sometimes alive and capable of becoming implanted on the endothelial surface of veins. If bits of endometrial tissue escape into veins during the menstrual reaction of ectopic endometrial tissue in the vaginal wall, we would expect that a similar condition might arise in ectopic endometrial tissue in any situation including a direct or primary endometriosis of the uterus.

FIG. 62. Photomicrograph (× 130) of a cross-section of a vein in the vaginal wall at a distance from the endometriosis shown in the preceding illustrations. The vein was situated in the lower part of the portion of the vagina which had been excised. A mural thrombus is present containing a bit of "endometrial tissue." We would expect that similar bits of endometrial tissue might escape into the general venous circulation and be carried to the lungs. The patient had as a postoperative complication, "a bronchopneumonia" from which she recovered. Is it possible that this might have been due to a "shower of endometrial tissue" disseminated by the trauma of the operation?



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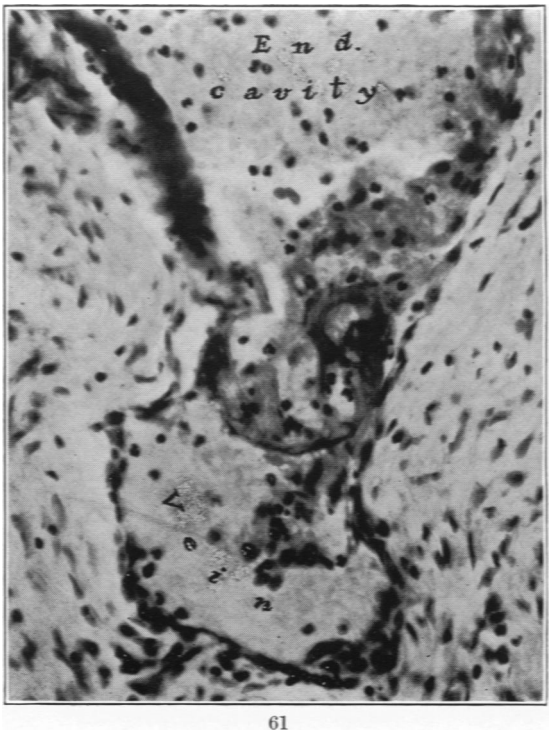

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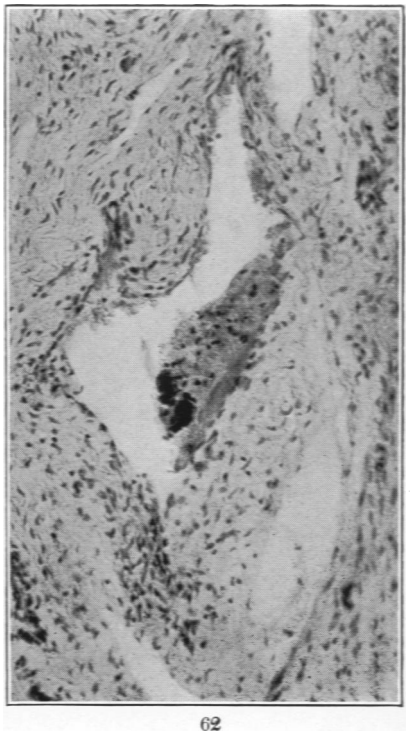

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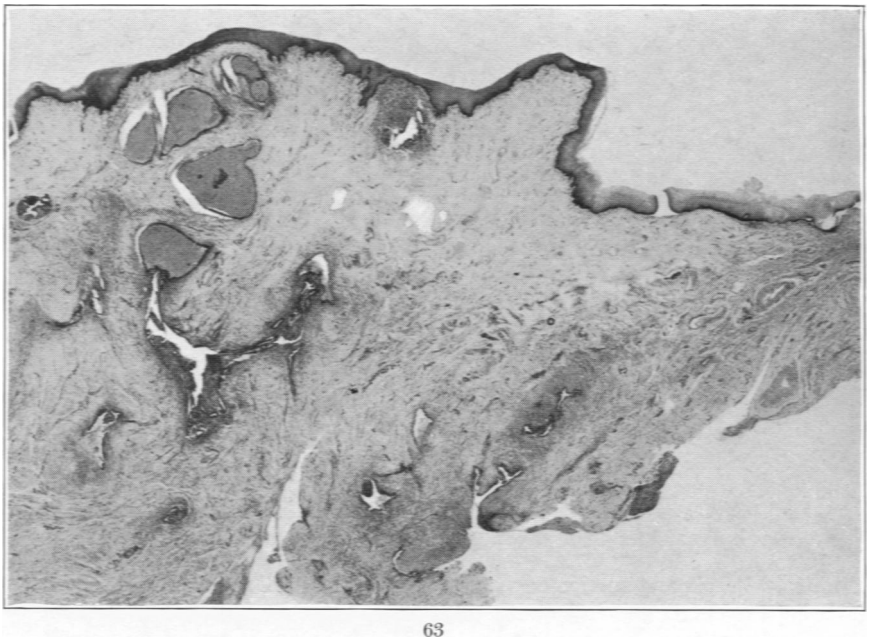
Sampson

Metastatic or Embolic Endometriosis

PLATE 40

FIG. 63. Photomicrograph (× 10) of another section of the vaginal wall again showing many endometrial lesions, including one just beneath and eroding the vaginal epithelium.

FIG. 64. Photomicrograph (× 25) of the vaginal wall from the same block as the preceding illustration demonstrating the erosive action of endometrial tissue on the vaginal epithelium. The endometrial cavity contains blood and bits of endometrial tissue set free by the menstrual reaction. In time the overlying vaginal epithelium might rupture and the contents of the cavity would escape into the vagina just as similar cavities in the ovary or any pelvic structure might rupture and their contents escape into the peritoneal cavity. The hemorrhagic areas of the posterior vaginal wall (see Fig. 67) are due to the accumulation of menstrual blood in these subepithelial endometrial cavities.



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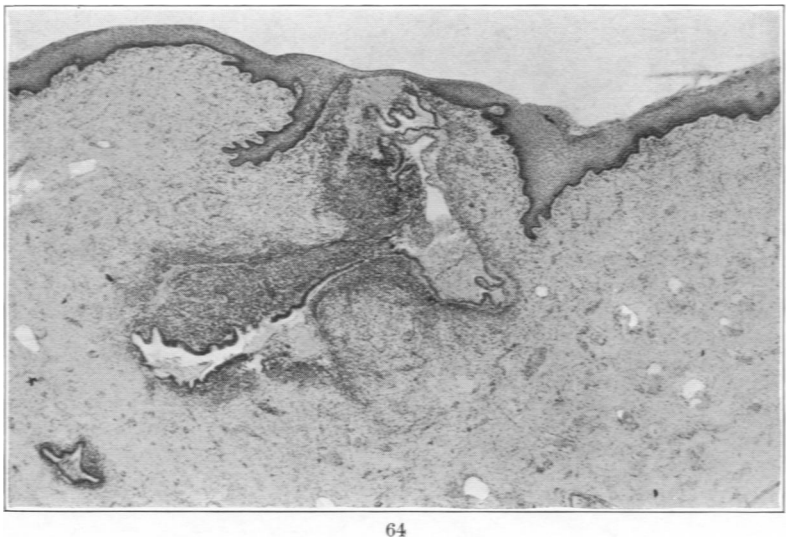

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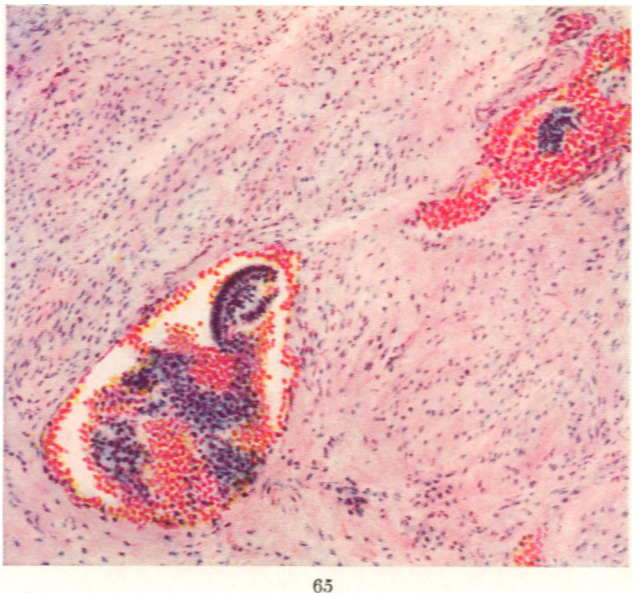
PLATE 41

FIG. 65. Colored photomicrograph (× 130) of a portion of the peripheral zone of the right half of the posterior uterine wall (Case 4). The patient was operated upon the second day of menstruation. Fragments of endometrial tissue (emboli) are present in two veins (probably two sections of one vein). It is natural to assume that they were set free by the menstrual reaction of either an embolic growth in a vein or else from the mucosa lining the uterine cavity. The implantation of such emboli in veins would give rise to lesions similar to those shown in Figs. 41, 49 and 52.

FIG. 66. Colored photomicrograph (× 130) of a portion of the posterior vaginal wall (Case 4) showing endometrial epithelium implanted in a vein, one of the veins indicated in Fig. 58 (see also Figs. 59, 60 and 61).

FIG. 67. Cervix and portion of the posterior vaginal wall (natural size) showing the characteristic appearance of the endometriosis in this situation. The hemorrhagic elevations are due to the accumulation of menstrual blood in subepithelial endometrial cavities (see Figs. 63 and 64).



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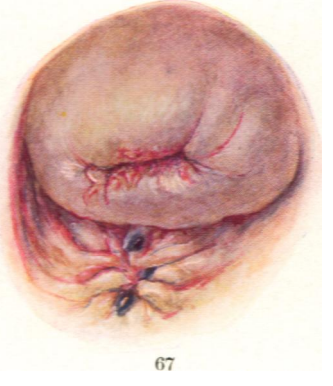

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